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A CLINICAL AND EXPERIMENTAL STUDY OF ISUPREL IN SPONTANEOUS AND INDUCED ASTHMA

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ONE of the synthetic analogues of epinephrine — 1-(3 , 4 -dihydroxyphenyl)-2-isopropylaminoethanol — has been studied under the name of aleudrin for a number of years in Europe. The experimental and clinical use of this drug in bronchial asthma and emphysema has been reviewed by Dautrebande,[1] and a report has been published in this country by Charlier.[2] The drug, administered as an aerosol, has been described as being especially effective in relieving attacks of bronchial asthma and significantly more active than epinephrine.

In this country Segal[3] has reported excellent results in the treatment of bronchial asthma with the same preparation, also called isuprel, and Siegmund et al.[4] found this drug to be the most active of a number of structurally related compounds in a study in guinea pigs using histamine and horse serum.

We have had occasion to observe the efficacy of isuprel in asthmatic patients in the outpatient clinic, among private patients on the hospital wards and also in association with experimental studies involving the induction of asthma-like attacks with histamine, acetyl-beta-methyl choline (methacholine) and certain allergenic extracts.

MATERIALS AND METHODS

Methacholine was injected intramuscularly in a concentration of 10 mg. per cubic centimeter, and histamine acid phosphate was injected intravenously in a concentration of 0.2 mg. per cubic centimeter. Allergenic extracts were prepared in phosphate buffer at a reaction of pH 7.4 containing 0.5 per cent phenol in a concentration of 1:20 by weight of dry pollen.

Isuprel§ was made available to us as a solution for administration by aerosol in a concentration of 1 and 0.5 per cent, in a concentration of 0.02 and 0.01 per cent for injection, and in tablets containing 10 mg. for sublingual administration. The effectiveness of these preparations in relieving the signs and symptoms in asthmatic subjects was studied by the following methods:

Asthmatic subjects using this agent were observed for relief of asthma on the hospital wards or at home. The effectiveness of treatment was judged chiefly by statements made by the patients and to a lesser extent by changes in physical signs. The use of other preparations was not specifically discouraged, and there were frequent cases in which the efficacy of isuprel could be compared with that of other agents with which the patient was familiar.

Subjects with asthma were observed in the laboratory during spontaneous attacks, and changes in vital capacity and physical signs, as well as the degree of subjective relief, were observed after the administration of isuprel.

Similar observations were made in asthma-like attacks induced by exposure to aerosolized allergenic extracts, histamine and methacholine and by injections of histamine and methacholine according to technics that have been described elsewhere.[5, 6]

The vaponephrin nebulizer or the No. 40 DeVilbiss nebulizer was used with a hand bulb by patients treating their asthmatic attacks outside the hospital, and these nebulizers supplied with pressure from an oxygen tank with the flow meter adjusted to read 6 to 8 liters per minute were also used on the ward and in the laboratory. Although the No. 40 DeVilbiss nebulizer may be somewhat less efficient than the vaponephrin nebulizer,[7] we observed no difference between the two types in our studies.

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§Kindly supplied by Winthrop-Stearns, Incorporated, Boston.

During administration of the various aerosols used in this study, patients were instructed to exhale forcibly, then to make a maximum inhalation and finally to hold their breath for a few seconds before exhaling. Vital-capacity measurements were made in the usual manner, and tracings of the expiratory curves were made on a moving drum. Care was taken to ensure maximum effort on the part of the patient. Maximum ventilatory volume was determined by the method of Hermannsen, which has been discussed in detail by Cournand, Richards and Darling.[8] A 9-liter Benedict–Roth type of metabolism apparatus was used, equipped with special low-resistance valves and with the container for soda lime removed. Computation of results was simplified by the addition to the machine of a recording ventilometer that measured inspiratory volume only.[9] A maximum ventilatory effort was made for fifteen seconds with the patient choosing his own rate and depth of respirations. Normal values for this method are approximately 150 liters per minute for male and 100 liters per minute for female subjects.

Results

Clinical Use of Isuprel

Thirty asthmatic patients were supplied with isuprel in a concentration of 0.5 per cent to be administered with a hand nebulizer at home. Ten of the 30 patients using the drug at home obtained excellent relief, 14 obtained good relief, 3 obtained fair relief, and 3 obtained practically no relief.

Ten of these 14 patients classified as having received good relief with isuprel stated that this was true only when the attacks of asthma were not severe. While under our observation and using isuprel at home, 7 of these patients developed severe asthma and required hospitalization. In this group 3 other patients, although they were not hospitalized, developed severe asthma with no benefit from isuprel and had to be treated by other measures. We could not determine why these changes occurred, but the severity of the asthma may have been the determining factor.

In addition to the 7 patients who had been using isuprel at home before hospitalization, there were 5 patients with severe asthma who received isuprel for the first time in the hospital. Of these 12 patients, 10 required, in addition to isuprel, intravenous injections of aminophylline, repeated doses of sedatives including demerol, infusions of glucose and saline solution, epinephrine and in some cases oxygen with or without helium.

The patients were not encouraged to continue using isuprel when repeated administration gave only very brief and incomplete relief. We are aware that much more intensive and prolonged administration of isuprel aerosol has been reported to be successful under these circumstances. When continued administration failed to produce subjective or objective improvement in the asthma of our patients, we abandoned this method of treatment and relied upon the procedures mentioned above. Patients in whom isuprel aerosol had become ineffective in relieving the more severe attacks of asthma frequently found that relief with isuprel was obtained from milder attacks occurring subsequently.

Two patients with severe asthma died unexpectedly. The cause of death appeared to be asthma. We were unable to determine what part, if any, isuprel played in these cases. They are presented in detail below.

Case Reports

Case 1. A 22-year-old married woman, 6 months pregnant, had been admitted to the Massachusetts Memorial Hospitals five times between March and July, 1947, because of severe bronchial asthma. Since early childhood she had suffered with hay fever in the summer and autumn. At the age of 12, during the ragweed season, she had her first attack of asthma, after which she had asthma perennially, with aggravation of symptoms during the pollinating seasons. On several occasions skin tests had shown positive reactions to cat hair, ragweed, birch, oak, grasses, beef, lobster and walnuts. Over the course of years she had used ephedrine, epinephrine, aminophylline, potassium iodide and barbiturates. She had also received injections of pollen extracts.

Early in 1947, when she was 2 months pregnant, she was seen because of a severe attack of asthma and given isuprel for the first time, to be used by inhalation. This preparation was very satisfactory, and relief lasted from hours to days. Weeks later, however, as the attacks of asthma became more continuous and severe, isuprel became less effective, producing relief lasting only minutes. The patient also failed to respond to repeated large doses of epinephrine and responded only to aminophylline given intravenously. Finally, relief obtained by intravenous injection of aminophylline was incomplete and transitory, and she was hospitalized on June 9, 1947.

Physical examination was not remarkable, except for moderate respiratory distress with a nonproductive cough, wheezes throughout both lung fields and a palpable uterus at the level of the umbilicus.

The blood Hinton reaction was negative, and there was no anemia. Examination of the blood revealed a white-cell count of 12,700, with 9 per cent eosinophils.

The asthma was controlled with intravenous injections of aminophylline, epinephrine administered subcutaneously, isuprel by inhalation and barbiturates at bedtime. The patient was discharged on July 3. Subsequently, she continued to have mild asthma, for which she used isuprel repeatedly.

The patient was last seen on the evening of July 9, when she appeared well. Shortly after midnight, because of asthma, she gave herself four subcutaneous injections of epinephrine, and during the following morning and afternoon additional injections of epinephrine were taken, the exact number of which is unknown. For sedation during the night of July 9 she apparently took a total of 0.4 gm. (6 gr.) of nembutal, and she may have taken some phenobarbital as well. During this time she continued to use isuprel. Her husband saw her at noon on July 10, and except for a rapid pulse, he did not find cause for alarm. Her mother saw her last about 3:55 p.m., when the patient did not appear in any distress. She went upstairs, and the mother followed about 5 minutes later upon hearing a thud. She found the patient lying on the floor, cyanotic, and breathing with great difficulty. She could not be aroused. Fifteen minutes later she died. Permission for autopsy was not obtained.

Case 2. A 32-year-old married man was admitted to the Massachusetts Memorial Hospitals on April 19, 1947, complaining of continuous asthma of 2 weeks' duration. His maternal aunt had asthma, and his brother had hay fever. He had had hay fever and bronchial asthma in the fall for 10 years. Treatment with ragweed-pollen extracts had given moderately good results. The asthma had been easily con-

trolled by small doses of ephedrine or epinephrine by injection. Skin tests performed in the fall of 1946 gave positive reactions to many pollens, animal danders and foods. One month prior to admission to the hospital he developed urticaria, which did not respond to epinephrine or benadryl, but finally cleared for no apparent reason.

Two weeks prior to admission he began having severe attacks of asthma with no response to ephedrine, epinephrine or aminophylline. At that time he was given isuprel for inhalation, which gave fairly good relief, sometimes lasting 1 or 2 hours. Gradually, however, this preparation became less and less effective, and the severity of the asthma increased so that finally he had to be admitted to the hospital.

Physical examination revealed a well developed and well nourished man in no acute distress who was wheezing moderately and appeared slightly apprehensive. Wheezes and squeaks were heard throughout both lung fields.

Examination of the blood showed a white-cell count of 7600, with 67 per cent granulocytes and 3 per cent eosinophils. The hematocrit was 48 per cent, and the hemoglobin was 15.7 gm. per 100 cc. The urine was normal, except for the slightest possible trace of albumin. X-ray study of the chest revealed slight emphysema.

Because of increasing asthma, the patient received repeated injections of epinephrine, which gave little relief. He also received aminophylline intravenously, to which he responded poorly. Aerosolized isuprel produced slight relief for brief periods. The asthma continued to increase in severity, and the patient became dyspneic and cyanotic.

On the 2nd day in the hospital, late in the afternoon, he complained of marked shortness of breath, and he was apprehensive. He received ether in oil by rectum, but because of lack of co-operation less than 30 cc. was given. He became comatose and remained so for about 2 hours until suddenly, at about 7:00 p.m., he changed color and the respirations became gasping in nature. Artificial respiration, as well as intracardial injection of epinephrine, was given to no avail. The patient was pronounced dead at 7:15 p.m.

At post-mortem examination* the heart weighed 355 gm. The endocardium was not remarkable, except for the anterior cusp of the mitral valve, which presented a small rectangular plaque of atheroma. The myocardium showed no evidence of fibrosis or infarction. The coronary arteries were palpable in their proximal few centimeters. There was a moderate degree of atheromatous change in the left and right coronary arteries and in the proximal few centimeters of their descending branches. The maximum amount of stenosis amounted to 50 per cent of the lumen. There was no evidence of coronary thrombosis or coronary occlusion.

The lungs together weighed 1760 gm. They were obviously bulky and voluminous. Their color was light pinkish yellow, with a faint reddish tinge that became more prominent in the lower lobes. The consistence of the lungs was quite rubbery, and they pitted easily on pressure. Moderate pressure produced deep pits, which disappeared slowly. Crepitation was elicited throughout but felt slightly reduced, and the normal spongy texture of the lungs was not felt. The trachea and bronchi contained a moderate amount of whitish, mucoid, very frothy material that did not occlude the lumens. The secondary branches of the major bronchi were completely occluded by bright-yellow, purulent, rather tenacious material, which formed plugs. In the smaller bronchi the plugs became firmer in consistence and assumed a brighter yellow appearance. These were found in perhaps half the bronchi and small branches in all lobes. On cut surface, the color of the parenchyma in all lobes was a light red, with tiny pinhead-sized, darker red, mottled patches scattered throughout the lobes. The pulmonary arteries were dissected and found free from thrombus.

The microscopical findings of asthma were striking. The bronchi and bronchioles showed some or all of the following changes. The lumens were partially filled with mucoid exudate, in which were embedded numerous desquamated epithelial cells, lymphocytes, eosinophils and bacteria. The epithelium in situ was often reduced to a layer one cell in thickness. Occasional squamous metaplasia was seen. Frequently, the mucosa was infiltrated with neutrophilic and eosinophilic polynuclear leukocytes. The basement membranes were thickened and hyalinized, and their refractile appearance was striking. The submucosa was densely infiltrated with lymphocytes and large mononuclear leukocytes. Scattered among these cells were many neutrophilic and eosinophilic polynuclear leukocytes. The inflammatory infiltrate extended into the bronchovascular connective tissue and very frequently formed a collar around small blood vessels. The infiltration also extended into the mucous glands in the bronchial walls. The glands were numerous and prominent. In many of the walls, the muscle bundles were thickened and very prominent. The bronchial and bronchiolar lumens were never completely occluded by exudate, although a few bronchioles were seen that were almost occluded by masses of eosinophils. No Curschmann spirals or Charcot-Leyden crystals were found.

The atria and alveoli were markedly distended in most areas. They were empty, except for an occasional large mononuclear anthracotic phagocyte or a few red blood cells. Very occasional patches of atelectasis were found. The alveolar walls were rather diffusely infiltrated with neutrophilic and eosinophilic polynuclear leukocytes.

The elastic-tissue stains showed marked fragmentation of elastic fibers in the lamina propria of the bronchi. In a few areas, the elastic tissue had disappeared altogether. The refractile, thickened basement membranes were striking in these preparations. The elastic-fiber proliferation in the intima of some of the arterioles and small arteries, with resulting thickening and narrowing of the lumen, was prominent. Many of the arteries showed reduplication and fragmentation of the elastic laminas.

*Performed by Dr. Israel Diamond.

Vital Capacity in Spontaneous Asthma

Observations were made in 23 subjects with spontaneous asthma. The vital capacity of each subject was determined, and any change after inhalations of isuprel was observed. An increase in vital capacity occurred in every case, and this was usually associated with subjective sensations of relief. As a rule the physical signs of asthma decreased, but in 1 case they increased in spite of a rise in vital capacity and a reduction in the subjective sensation of asthma. In most cases in which small increases occurred, the vital capacity was close to the maximum vital capacity for the patient, as judged by values obtained at periods when no asthma was present. One exception was a patient who was followed during a period in which her symptoms were especially severe. Her maximum vital capacity had been observed earlier to be 2700 cc. On the present occasion her vital capacity was 1500 cc., and after fifteen inhalations of isuprel, it was 1550 cc. The subsequent intravenous injection of aminophylline likewise failed to increase the vital capacity.

Comparative Effectiveness of Isuprel and Other Drugs

In a few cases there was opportunity to compare the efficacy of isuprel administered by inhalation with that of epinephrine by inhalation (1:100 solution) and injected subcutaneously (1:1000 solution) and aminophylline given intravenously. We recognized the fact that patients may overestimate the efficacy of a new preparation when it is first used and that some of what follows is perhaps best regarded with this tendency in mind.

One subject received five inhalations of epinephrine 1:100 with an increase in vital capacity from 2150 to 2700 cc. A second series of five inhalations caused a further rise of only 50 cc. The subcutaneous administration of 0.3 cc. of epinephrine

(1:1000 solution) caused no further increase in vital capacity in a period of ten minutes. Five inhalations of isuprel (1 per cent) then caused an increase to 3050, and a second series of five inhalations caused a further increase to 3700 cc.

In another subject receiving isuprel for the first time, inhalations of the drug (1 per cent) were given repeatedly over a period of thirty minutes. Marked relief of asthmatic symptoms occurred — the best in many weeks. On the following day the inhalations were repeated, but epinephrine (1:100 solution) was substituted for the isuprel without the patient's knowledge. Little relief occurred, and the patient was greatly disappointed. On the third day isuprel was again given, with excellent relief. No vital-capacity studies were made in this patient.

Although most patients who used both epinephrine and isuprel as aerosols stated that the latter was consistently superior, 4 patients stated that epinephrine was as good as isuprel or better, after having had considerable experience with both. The epinephrine preparation used in some cases was a proprietary product containing the drug in a concentration of 2 per cent.

Aminophylline

On numerous occasions patients who were admitted to the hospital for treatment of asthma received both isuprel by inhalation and aminophylline intravenously in doses of 0.25 or 0.48 gm. Although no studies of vital capacity were made, the very definite impression was obtained that aminophylline injected intravenously was superior to isuprel for the treatment of severe asthma. Subjective relief was not only greater but also more prolonged. Experience with aminophylline given by other routes has been limited and is difficult to evaluate.

Relief from Attacks Induced by Inhaled Allergenic Extracts

Observations were made in 9 asthmatic subjects in whom asthma-like attacks were induced by exposure to various aerosolized allergenic extracts by inhalation.[10–12] As shown in Table 1, the administration of isuprel caused a rapid return of the vital-capacity readings toward normal. In some cases pyribenzamine or atropine had been given with a view to possible protection of the patient from the expected decrease in vital capacity or in an attempt to restore the vital capacity after this had been reduced by exposure to an aerosolized pollen extract. Isuprel was effective in every case but 1, whereas intravenously administered atropine was without influence or had a very slight effect and intravenously administered pyribenzamine rarely influenced the vital capacity under the circumstances of the test. Interpretation of results obtained with tests of this kind is complicated by the tendency of the vital capacity to return toward normal without any treatment. However, inspection of the records obtained in these experiments afforded convincing evidence that inhalation of isuprel was chiefly responsible for the observed rapid increases in vital capacity.

Table 1. *Effect of Inhalations of Isuprel in Restoring the Vital Capacity after Experimental Reduction by Inhalation of Aerosolized Allergenic Extracts.*

Case No.	Age	Sex	Maximum Vital Capacity	Allergenic Extract	Interval after Exposure to Extracts	Vital Capacity after Inhalation of Extract	Interval after Exposure to Isuprel	No. of Inhalations of Isuprel	Vital Capacity after Inhalation of Isuprel
	yr.		*cc.*		*min.*	*cc.*	*min.*	*0.5%*	*cc.*
1	42	F	2,700	Birch pollen	23	1400	6	6*	2125
				Oak pollen	60	1300	4	5	2100
				Birch pollen	34	2150	6	10	2600
				Oak pollen	112	2225	112	11	2700
				Oak pollen	72	1900	13	12*	2700
2	45	F	2,800	Ragweed pollen	20	1750	1	5	2300
3	37	F	2,800	Birch pollen	15	1175	4	10	2225
				Ragweed pollen	124	1900	½	5	2125
4	37	F	3,050	Oak pollen	7–67	1100	†	27	2800
				House dust	40	2500	3	5	3150
				Timothy pollen	15	2700	1	5	3050
5	22	F	3,700	Ragweed pollen	49	3300	½	4	3700
6	48	M	4,000	House dust	14	3000	1	6	4000
7	48	F	2,550	House dust	9	900	4	5	2400
8	38	M	4,500	Birch pollen	17	3650	½	5	4700
				Ragweed pollen	35	3750	½	5	4450
				Ragweed pollen	27	3650	6	5	4300
				Oak pollen	17	3500	1	5	4400
				Ash pollen	20	3700	5	5	4100
9	15	M	3,100	House dust	9	1700	4	6	2650

*1 per cent isuprel solution administered.
†Inhalations of isuprel given over a period of 52 minutes.

Effect of Isuprel in Preventing the Reduction in Vital Capacity and Asthma-like Attacks due to Parenterally Administered Histamine and Methacholine

Experiments were carried out in which the effect of isuprel administered parenterally on two occa-

sions and by aerosol on another occasion was observed for evidence of any resulting change in the subjects' susceptibility to injected histamine or methacholine as determined by changes in vital capacity.[5, 6]

In 1 subject the resting vital capacity was 3072 cc. and the intravenous injection of 0.02 mg. of histamine base produced an asthma-like attack with a reduction of 952 cc. in the vital capacity. This type of response occurs in the great majority of asthmatic subjects. In twenty minutes the attack disappeared, and the vital capacity was 3062 cc. A dose of 0.1 mg. of isuprel was then given intramuscularly, and within two minutes the pulse was bounding and the rate had increased from 80 to 120 per minute. Marked nervousness, palpitation and faintness were experienced, but these symptoms disappeared within ten minutes, and at this time the vital capacity measured 3103 cc. A second injection of 0.02 mg. of histamine base produced no subjective or objective signs or symptoms in the chest, and the vital capacity was not reduced. However, other systemic effects of histamine, such as the gaseous taste in the mouth, flushing and headache, were not prevented by administration of isuprel. A third injection of 0.02 mg. of histamine base thirty minutes after isuprel induced slight wheezing in the chest, with a reduction of 920 cc. in the vital capacity. It was apparent that isuprel blocked the action of histamine in a manner similar to that of epinephrine,[13] but its action was short-lived. In this subject 0.1 mg. of epinephrine produced no side effects and completely blocked the respiratory effects of 0.02 mg. of histamine base after thirty minutes, and some histamine-blocking effect was still demonstrable after sixty minutes.

In another subject, with a resting vital capacity of 4253 cc., the intramuscular injection of 6 mg. of methacholine induced an asthma-like attack, with a fall of 1003 cc. in the vital capacity. In fifteen minutes the attack had abated and 0.06 mg. of isuprel given intramuscularly was followed in a few minutes by palpitation, a rise in pulse rate to 170 per minute and a fall in blood pressure to 70 systolic, 60 diastolic, from the previous level of 120 systolic, 80 diastolic. Eight minutes after the administration of isuprel the vital capacity was 4128 cc. A second intramuscular injection of 6 mg. of methacholine produced no subjective or objective changes in the chest, nor was there a significant reduction in vital capacity. However, when the dose of methacholine was repeated thirty minutes after the administration of isuprel, the reaction produced was similar to that before the isuprel had been given. Thus, as in the previous case with histamine, the blocking action of isuprel against methacholine was lost within thirty minutes of the administration of isuprel.

In a third experiment, the subject came to the laboratory with a spontaneous attack of asthma. Four vital-capacity tests averaged 2633 cc. In a period of thirty-eight minutes twenty-four inhalations of isuprel were administered without any side effects, and the vital capacity increased to 3688 cc. At this time 0.02 mg. of histamine base given intravenously caused a slight decrease in the vital capacity, and fifteen minutes later 3 mg. of methacholine given intramuscularly produced no reduction in vital capacity (Fig. 1). In previous studies in this subject the same doses of histamine and methacholine caused pronounced reductions in the vital capacity.

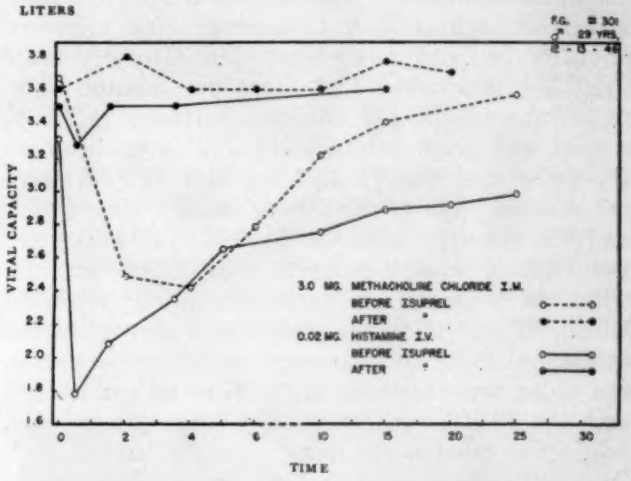

FIGURE 1. *Effect of Isuprel Aerosol on the Pulmonary Response to Methacholine and Histamine.*

The curves with the open circles show the effect of injected histamine base and methacholine on the vital capacity. On another occasion, when twenty-four inhalations of isuprel (1:100 solution) had been given for relief of asthma, the tests were repeated, with the results shown by the curves with solid circles. The time is given in minutes elapsed after the administration of histamine and methacholine.

These studies, though few in number, indicate that isuprel furnishes potent protection against the reduction in vital capacity and asthma-like attacks induced by the parenteral administration of histamine and methacholine. Our experience with the intramuscular use of isuprel is obviously limited, but the short-lived protection afforded against histamine and methacholine together, with the degree of side reactions produced by the drug as compared to intramuscular injections of epinephrine, discouraged us from further studies.

Sublingual Administration of Isuprel

Our experience with the sublingual use of isuprel is limited to observations in 13 patients receiving the drug by this route for relief of symptoms at home and in 2 subjects studied in the laboratory.

Patients receiving tablets of isuprel sublingually at home were instructed to take one tablet containing 10 mg. at thirty-minute intervals until relief

had occurred or until four tablets had been taken in any one day. Of these 13 patients, 3 who were suffering from mild asthma stated that they had obtained excellent relief after taking one or two tablets. Five patients had asthma of moderate severity, and of these, 2 stated that the drug was without effect and the remaining 3 obtained relief of very short duration even with doses as large as 50 mg. in two hours. The 5 remaining patients who had severe asthma denied benefit with similar doses.

Two patients with spontaneous asthma were studied in the laboratory. One subject arrived in a mild attack of asthma with an average vital capacity of 2289 cc. and a maximal ventilatory volume (M.V.V.) measuring 33.4 liters per minute. The pulse rate was 66 per minute. A 10-mg. tablet of isuprel was given sublingually, and in ten minutes the pulse rate was 72 and the M.V.V. 37.6 liters per minute. Again, two 10-mg. tablets were given, and ten minutes later the M.V.V. was 48.0 liters per minute, with a pulse rate of 88 per minute. Thus, in a period of forty-eight minutes during which 50 mg. of isuprel was administered by the sublingual route no side reactions were experienced, the pulse rate increased from 66 to 88 per minute and the M.V.V. increased 14.1 liters per minute. Subjective relief of the asthma was also experienced. At the end of this period twelve inhalations of isuprel were followed by an increase in M.V.V. to 54.3 liters per minute and the vital capacity was 2874 cc.

In the other subject, spontaneous asthma was present and the M.V.V. measured 45.0 liters and the pulse 120 per minute. At ten-minute intervals a tablet containing 10 mg. of isuprel was placed under the tongue until 70 mg. had been given. The pulse rate gradually decreased to 104 per minute, and the M.V.V. increased to 65.8 liters per minute. When eight inhalations of isuprel were given, however, there was a rapid increase in M.V.V. to 75.2 liters per minute within ten minutes.

These two experiments suggest that isuprel was not very effective when administered by the sublingual route, except perhaps with large doses. No side reactions were experienced with doses of 50 and 70 mg. respectively despite the fact that palpitation and tachycardia were noted after intramuscular doses of the drug as low as 0.1 mg. We recognize the possibility that the physical characteristics of the sublingual tablets and the success patients may have in preventing themselves from swallowing while holding the tablet under the tongue are important factors in the results obtained in studies of this kind.

Side Effects

Administration by Aerosol

Only 2 patients in this series of 30 asthmatic subjects experienced symptoms that might reasonably be attributed to inhalation of isuprel. In each case nervousness, tachycardia and palpitation were experienced, lasting only a few minutes. In 1 case this followed fifteen inhalations of isuprel (1:100 solution), and in the other, these symptoms followed repeated groups of five to ten inhalations of isuprel (1:200 solution) at short intervals. Both patients used isuprel on other occasions without difficulty.

Sublingual Administration

No side reactions other than a bitter taste were observed in the 15 patients receiving tablets containing 10 mg. of isuprel in amounts up to 70 mg. within a period of an hour or more. A normal subject receiving one 10-mg. tablet sublingually experienced flushing and headache with slight malaise lasting about an hour.

Parenteral Administration

In 5 cases in which isuprel was given subcutaneously or intramuscularly, 2 of which were described above, side reactions were observed. These were tachycardia, palpitation and nervousness in all cases, a fall in blood pressure in 1 case and pallor, nausea and a rise in blood pressure in another. These reactions were not associated with any change in the lung that could not have been readily obtained with isuprel administered by aerosol or with other agents causing fewer or no side effects.

Summary

Isuprel, 1-(3′, 4′-dihydroxyphenyl)-2-isopropylaminoethanol, was administered to asthmatic subjects in the outpatient clinic, on the wards and in the laboratory. In most cases the drug was given as an aerosol, but some observations were made in which the drug was given by the sublingual and subcutaneous routes.

The drug given as an aerosol was very effective in relieving mild or moderately severe asthma and appears to be the most effective agent available for self-medication. However, in severe and prolonged attacks of asthma, the drug was far less satisfactory. In certain cases other medications, particularly intravenously administered aminophylline, were required. With recovery, isuprel was again effective in the control of milder attacks. Side effects were uncommon with the doses used in the study.

References

1. Dautrebande, L. *Aérosols médicamenteux: technique — physiologie — thérapeutique.* 207 pp. Paris: Masson et Cie, 1946.
2. Charlier, R. Therapeutic studies in bronchial asthma with aerosols of aleudrin. *M. Times* **75**:277-286, 1947.
3. Segal, M. S., and Beakey, J. F. The use of isuprel for the management of bronchial asthma. *Bull. New Eng. M. Center* **9**:62-67, 1947.
4. Siegmund, O. H., Granger, H. R., and Landa, A. M. Bronchodilator action of compounds structurally related to epinephrine. *J. Pharmacol. & Exper. Therap.* **90**:254-259, 1947.

5. Curry, J. J. Action of histamine on respiratory tract in normal and asthmatic subjects. *J. Clin. Investigation* **25**:785-791, 1946.
6. *Idem.* Comparative action of acetyl-beta-methyl choline and histamine on respiratory tract in normals, patients with hay fever, and subjects with bronchial asthma. *J. Clin. Investigation* **26**:430-438, 1947.
7. Abramson, H. A. Principles and practice of aerosol therapy of lungs and bronchi. *Ann. Allergy* **4**:440-456, 1946.
8. Cournand, A., Richards, D. W., Jr., and Darling, R. C. Graphic tracings of respiration in study of pulmonary disease. *Am. Rev. Tuberc.* **40**:487-516, 1939.
9. Reichert, P. Recording ventilometer. *J. Aviation Med.* **7**:169-171, 1936.
10. Lowell, F. C., and Schiller, I. W. Reduction in vital capacity of asthmatic subjects following exposure to aerosolized pollen extracts. *Science* **105**:317, 1947.
11. Schiller, I. W., and Lowell, F. C. Effect of drugs in modifying response of asthmatic subjects to inhalation of pollen extracts as determined by vital capacity measurements. *Ann. Allergy* **5**:564-566, 1947.
12. Lowell, F. C., and Schiller, I. W. Measurements of changes in vital capacity as means of detecting pulmonary reactions to inhaled aerosolized allergenic extracts in asthmatic subjects. *J. Allergy* **19**:100-107, 1948.
13. Curry, J. J. Effect of antihistaminic substances and other drugs on histamine bronchoconstriction in asthmatic subjects. *J. Clin. Investigation* **25**:792-799, 1946.

THE DIAGNOSIS OF CONGENITAL ANEURYSM OF THE PULMONARY ARTERY*

Report of Two Cases

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NEW YORK CITY

THE literature is filled with accounts of dilatations or aneurysms of the pulmonary artery. Notable reviews of the literature have been written by Brenner,[1] Boyd and McGavack[2] and, recently, Deterling and Clagett.[3] Among the factors commonly accepted as causes of pulmonary-artery dilatation and aneurysm are infectious processes (such as syphilis and mycotic infection), congenital defects causing secondary dilatation (septal patency, patent ductus arteriosus, pulmonic stenosis, transposition of the great vessels and other less common lesions), rheumatic mitral stenosis, a variety of chronic pulmonary diseases that may cause pulmonary hypertension, thoracic deformities, cardiac failure and possibly trauma.

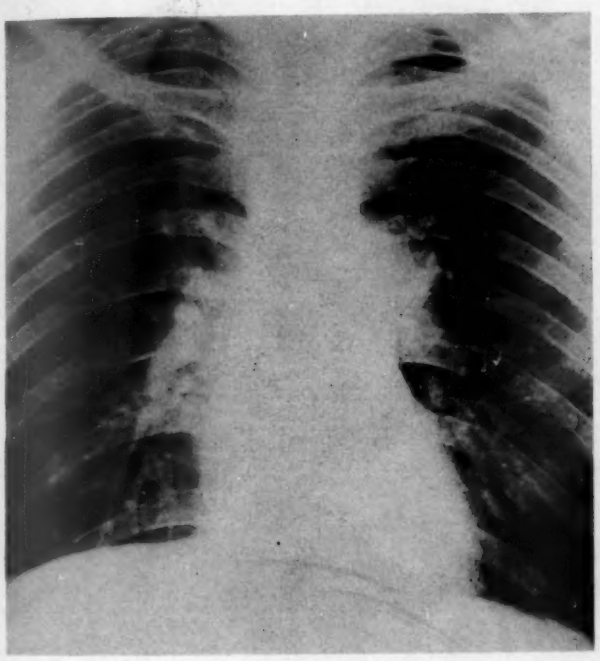

FIGURE 1. *Case 1. Conventional Roentgenogram (Frontal Projection).*
Note the prominent area of density in the left hilar region.

FIGURE 2. *Case 1. Angiocardiogram (Frontal Projection Three Seconds after Injection).*
Note that the left hilar shadow is opacified and shown to be a markedly dilated main-stem pulmonary artery and its left branch.

By our definition, congenital pulmonary-artery aneurysm is an organic, localized or diffuse aneurysmal dilatation of the pulmonary artery that can-

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not be accounted for by any of the known causes of pulmonary-artery dilatation. In a given case, the diagnosis cannot be entertained until these factors can be excluded. Many of the cases cited in the literature as aneurysms of the pulmonary artery are associated with such factors, and cannot be

FIGURE 3. *Case 1. Angiocardiogram (Left Lateral Projection Three Seconds after the Beginning of Injection).*

Superior vena cava, right atrium and superimposed right ventricle, pulmonary artery and left branch are well shown. Note the aneurysmal dilatation of the main stem and left pulmonary artery.

considered to represent congenital conditions. It is difficult to state the dividing line between simple and aneurysmal dilatation of a vessel. Since histologic examination cannot be made during life, and since the vessel wall in congenital aneurysm of the pulmonary artery would probably resemble the normal structure histologically, size remains the most effective criterion. For practical purposes, we refer to a major diffuse dilatation of an artery as aneurysmal. If the dilatation is sharply localized, it is referred to as an aneurysm.

Simple isolated aneurysmal dilatation of the pulmonary artery has been called "idiopathic."[4, 5] Actually, it is no more idiopathic than a septal defect in that both conditions are true congenital malformations. Angiocardiography has made it possible to delineate pulmonary-artery lesions accurately and to exclude many of the more frequently encountered causes of dilatation.[6] An angiocardiographic study of the normal pulmonary artery has made possible the more accurate evaluation of abnormal findings.[7] Over a period of eleven years, angiocardiographic visualizations on more than 650 patients have been accomplished. Of these cases, the clinical and roentgenologic features of 2 allow their classification as congenital pulmonary-artery aneurysms.

CASE REPORTS

CASE 1. A 34-year-old truckman was referred for angiocardiography in 1941 because of a prominence at the left hilus seen in a routine preinduction chest roentgenogram. The past and family histories were unremarkable; birth and development had been entirely normal. At the time of examination he was employed as a truckman and experienced no difficulty in doing manual labor. He recalled that he had been refused a job at the age of 22 because a chest film had shown "something around the heart." There was no history of rheumatic fever, and venereal disease was denied.

Physical examination revealed a well developed man whose only significant findings included an accentuated pulmonic second sound, a systolic murmur at the third left

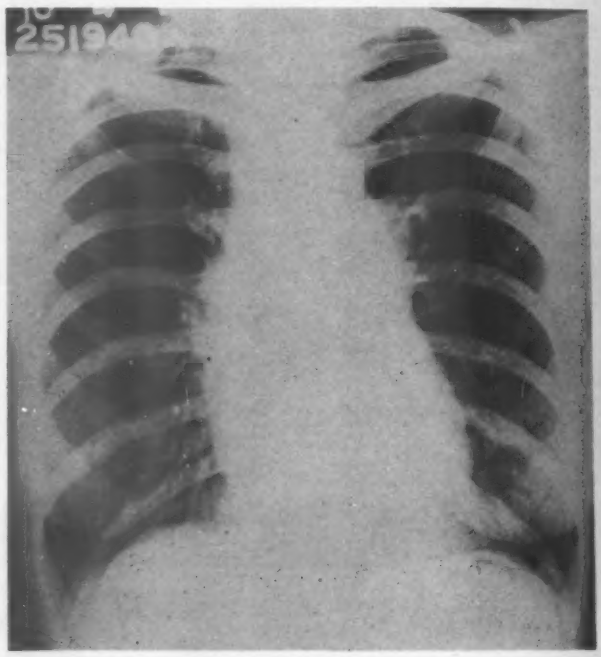

FIGURE 4. *Case 2. Conventional Roentgenogram (Frontal Projection).*

Note the prominent left hilar shadow, which was erroneously interpreted as enlarged hilar lymph nodes.

interspace and in the pulmonic area, and a basal diastolic murmur. The blood pressure was 120/80. Laboratory study, including a complete blood count and Wassermann examination, was negative.

A conventional roentgenogram of the chest (Fig. 1) showed a marked bulge of the pulmonary-artery segment on frontal projection that fluoroscopy disclosed to have an expansile systolic pulsation. On lateral projection, a rounded area of density was seen in the midst of the hilar shadows. The lung fields were clear, and the heart was not enlarged.

Angiocardiography (Fig. 2 and 3) revealed the opacification of an aneurysmal dilatation of the main-stem pulmonary artery and its left main branch. This measured 62 mm. in

its greatest superoinferior dimension, and was best seen in the lateral projection. The remainder of the visualization was entirely unremarkable. There was no evidence of septal defect, patent ductus arteriosus, pulmonic stenosis or other congenital cardiac abnormality. The patient continues to be asymptomatic.

Case 2. A 50-year-old housewife with an otherwise unremarkable past history was thought to have had tuberculous cervical lymphadenitis at the age of 44, evidenced by a painless swelling beneath the left mandible, which disappeared after the aspiration of sterile white fluid containing a moderate number of leukocytes. Culture for tubercle bacilli was negative. At that time x-ray examination of the lung fields was negative, but a prominence in the left hilus was interpreted as tuberculous hilar lymphadenopathy. Over a 6-year period there was no detectable change in the appearance of the left hilar shadow, and angiocardiography was then done to rule out the presence of abnormality of the pulmonary artery. At the time of visualization, the patient was asymptomatic.

Physical examination revealed an apparently healthy woman. A few small lymph nodes were felt in the cervical regions, but these were not thought to be significant. Auscultation of the heart revealed the presence of a blowing Grade III systolic murmur in the second and third intercostal spaces to the left of the sternum. The pulmonic second sound was accentuated. There were no other murmurs. The

Figure 5. *Case 2. Angiocardiogram (Frontal Projection Three Seconds after Injection).*

Neo-iopax outlines a dilated main-stem pulmonary artery and its left main branch, which make up the left hilar shadow.

remainder of the physical examination was unremarkable, as were laboratory studies, including a complete blood count and Wassermann test. An electrocardiogram showed slight left-axis deviation.

Conventional chest roentgenogram revealed an apparently normal heart and clear lung fields. In the middle portion of the left cardiac border, a prominent, convex shadow that extended out into the left lung field (Fig. 4) was seen. On fluoroscopic examination, this was found to have an expansile systolic pulsation. In the lateral projection, a rounded area of density was observed in the mid-hilar region.

Angiocardiography in frontal and lateral projections (Fig. 5 and 6) outlined an aneurysmal dilatation of the main-stem and both main branches of the pulmonary artery that measured 60 mm. in its greatest superoinferior dimension (measured in the lateral projection). The remainder of the contrast study was entirely unremarkable and failed to show evidence of associated congenital anomaly. The patient is

Figure 6. *Case 2. Angiocardiogram (Left Lateral Projection Three Seconds after Injection).*

The right ventricle, pulmonary conus and pulmonary artery and its left branch are well shown. Note the aneurysmal dilatation of the main-stem pulmonary artery and its left branch.

at present doing her housekeeping without difficulty and is free of symptoms.

Discussion

An attempt has been made to state the diagnostic criteria for congenital aneurysm of the pulmonary artery. This diagnosis is made by the demonstration of aneurysmal dilatation and by exclusion of the known factors causing such dilatation. Since the assumption is generally accepted that the condition is a true congenital malformation, the term "idiopathic" cannot be applied to it. It is suggested that the condition be termed congenital pulmonary-artery aneurysm, the title implying the presence of an uncomplicated or isolated congenital aneurysm.

The 2 cases reported above fulfill the criteria for this diagnosis. Both patients were asymptomatic, and it is assumed that symptoms would be caused by congenital pulmonary aneurysm only when the aneurysm was of sufficient size to produce compression of adjacent structures. Taussig[5] reports such a case. Surgical intervention in this condition is contraindicated.

Summary and Conclusions

The diagnosis of congenital pulmonary-artery aneurysm may be made in the presence of an

aneurysm or aneurysmal dilatation of the pulmonary artery that cannot be accounted for by associated congenital or acquired factors capable of causing pulmonary-artery dilatation.

Pressure studies by cardiac catheterization should be carried out whenever possible. The presence of an abnormally high pulmonary-artery pressure must be considered evidence against a congenital pulmonary-artery aneurysm. These studies will be conducted in Case 2.

Angiocardiography adequately demonstrates the nature of the dilatation and aids in excluding other causes of such dilatation.

It is suggested that the term "idiopathic" is misleading and should not be applied to a condition of congenital origin.

Two cases fulfilling these diagnostic criteria are presented.

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References

1. Brenner, O. Pathology of vessels of pulmonary circulation. *Arch. Int. Med.* **56**:211-237, 457-497, 724-752 and 1189-1241, 1935.
2. Boyd, L. J., and McGavack, T. H. Aneurysm of pulmonary artery: review of literature and report of two new cases. *Am. Heart J.* **18**: 562-578, 1939.
3. Deterling, R. A., and Clagett, O. T. Aneurysm of pulmonary artery: review of literature and report of case. *Am. Heart J.* **34**:471-499, 1947.
4. Oppenheimer, B. S. Idiopathic dilatation of pulmonary artery, *Tr. A. Am. Physicians* **48**:290-297, 1933.
5. Taussig, H. B. *Congenital Malformations of the Heart.* 681 pp. New York: Commonwealth Fund, 1947. P. 377.
6. Dotter, C. T., and Steinberg, I. Angiocardiographic study of pulmonary artery. *J. A. M. A.* (in press).
7. *Idem.* Angiocardiographic measurement of normal great blood vessels. *Radiology* (in press).

MULTIPLE SITES FOR BONE-MARROW PUNCTURE, WITH PARTICULAR REFERENCE TO CHILDREN*

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EXAMINATION of the bone marrow in hematologic disorders by means of puncture aspiration has become in this laboratory and in many others a routine study that is often invaluable in diagnosis. Although the sternum is the usual site of such puncture, several investigators have suggested other areas. Thus Van den Berghe and Blitstein[1] and Rubenstein[2] have stressed the value of the iliac-crest puncture, and more recently Loge[3] and Huss, Gilbert and Liebow[4] have advocated the spinous process as a site for obtaining a specimen of the bone marrow. Since alternative sites are often desirable we have investigated their value during the past year. Our observations in adults confirm those of the above investigators that essentially similar material is obtained from the various sites taken simultaneously. More recently we have applied the same technics in infants and children and have found that iliac-crest and vertebral punctures are especially valuable in these groups. In infants particularly, the sternal-marrow cavity is quite shallow, and the possibility of perforation into the mediastinum, although remote, is always present. Puncture of the tibial marrow in older children is often unsatisfactory. Furthermore, spinous-process puncture is often preferable for psychic reasons, since the child cannot see the activities associated with the procedure and consequently becomes less alarmed.

Figure 1. *Iliac-Crest Puncture, Showing the Position of the Needle (Gauge 16) at the Termination of the Puncture.*

Method

The same type of stiletted needle is used for the iliac-crest and spinous-process punctures as previously used for the sternal approach.¶ The needle has a total length of 6.7 cm. and a shaft of 3.3 cm. For *spinous-process puncture*, particularly in infants, a No. 1 gauge needle of the above dimensions is preferable. In infants and in young children, light anesthesia as obtained with a few whiffs of ethyl chloride is often useful.

The *iliac crest puncture* is performed after the area about the iliac crest has been prepared with

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¶This needle, ordinarily supplied as No. 16 gauge, may be purchased from the Hub Needle Company, Boston, Massachusetts.

iodine and then alcohol. The skin, subcutaneous tissues and periosteum are infiltrated with novocain in a small area just below the iliac crest. The bone-marrow needle is then pushed into the ilium distal to the crest (Fig. 1). One usually feels a distinct sense of "give," at which time the stilet is removed, a 10-cc. dry syringe is attached and a small amount (0.1 to 0.3 cc.) of bone-marrow material is aspirated. Smears are then made directly on specially cleaned glass slides, which are tilted so that most of the blood in the material becomes separated from the flecks of marrow that remain attached to the slide. Then, with the use of the end of another slide, a small portion of the marrow is picked up and smeared gently, with as little pressure as possible, on a third slide. Staining is carried out with a combination of Wright and Giemsa stains.

The *spinous-process puncture* is performed with the patient lying face downward, rather than in the sitting position as recommended by Loge.[3] This seems preferable for several reasons. Firstly, the necessary pressure can be more readily employed in the downward than in the horizontal plane. Secondly, the patient lies in a relatively fixed and more comfortable position and cannot be readily moved by the pressure applied. Finally, although the spinous process may be less prominent in the prone than in the sitting and flexed positions, it is easier to isolate and define individually. These reasons are particularly valid in the child. We have utilized a variety of spinous processes and have found that the lower thoracic vertebras and the lumbar vertebras are most satisfactory. The patient is prepared with iodine and then alcohol. The spinous process to be utilized is grasped on either side with the thumb and forefinger of the left hand, and the skin, subcutaneous tissue and periosteum are infiltrated with novocain. The bone-marrow needle is then introduced perpendicularly to the process, and after the sense of "give" is felt a syringe is attached and the material withdrawn (Fig. 2).

Results

In adults, bone-marrow punctures using multiple sites were performed in 31 patients. Spinous-process punctures alone were done in 25 additional cases. Of the patients with multiple punctures, 3 had sternal, iliac-crest and spinous-process punctures. Comparison of the results obtained with multiple punctures showed surprisingly similar findings, both in the general appearance of the marrow on microscopical study and in the differential counts. Occasionally, marrow was obtained from one site, when another yielded a dry tap. In 3 of our adult cases, multiple punctures revealed hypoplastic or aplastic marrow in three different areas. In 2 of these cases the finding was verified by trephine biopsy. Because of these highly comparable results in different areas, we now utilize the various sites interchangeably when multiple punctures are performed.

Spinous-process punctures were performed in 25 infants and children ranging from two months to twelve years of age. In 5 children two punctures were done. The iliac-crest puncture was performed in 8. Ten patients had both sternal and spinous-process punctures; 2 patients had sternal, spinous-process and iliac-crest punctures; 2 had iliac-crest and spinous-process punctures, and 1 had a tibial puncture in addition to punctures of the sternum and of a spinous process.

Of the 13 patients who had punctures at multiple sites, comparable results were obtained in 10.

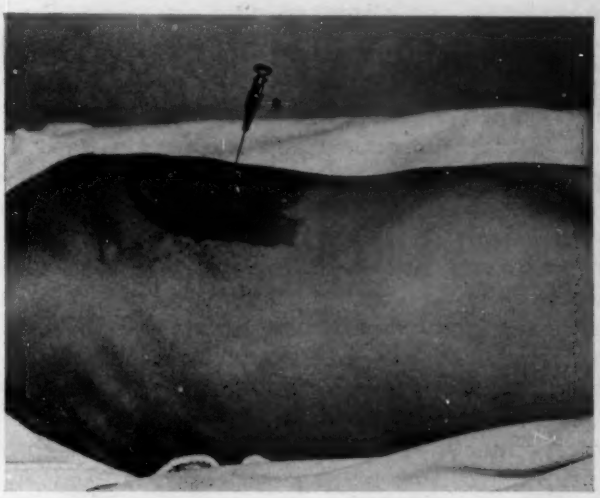

Figure 2. *Spinous-Process Puncture of an Upper Lumbar Vertebra in an Eight-Year-Old Child, Showing the Position of the Needle (Gauge 18) at the End of the Puncture.*

In the other 3 cases a diagnosis was made only when multiple punctures were performed. These cases are presented briefly, as follows:

R. C., an 11-year-old child, had possible aleukemic leukemia. Sternal puncture yielded a dry tap. Spinous-process puncture produced a small amount of very thick marrow showing an almost pure culture of lymphoblasts. Apparently, the marrow cavity was packed with very thick marrow, which resisted aspiration. It is possible that a second sternal puncture would have revealed similar findings, but the patient was spared this second puncture of an already sensitive sternum by performance of aspiration at an alternate site.

R. H., a 2-month-old infant, had thrombocytopenic purpura. Tibial puncture yielded no marrow, and two sternal punctures produced very dilute material, suggesting a hypoplastic marrow as the cause of the purpura. A spinous-process puncture revealed an essentially normal marrow, and the infant subsequently made an uneventful recovery. The final conclusion was that the purpura had been of infectious origin.

D. M., who was 3 years and 4 months old, was studied for possible leukemia, aleukemic variety. A sternal puncture and two spinous-process punctures revealed no marrow material. Puncture of the right iliac crest produced material that showed marked infiltration with early lymphoid cells,

and the diagnosis of acute lymphatic leukemia was made. Here again, the dry taps were probably the result of a very thickly packed marrow, which resisted aspiration.

Two cases in this series demonstrate the value of using multiple sites for confirmation of the results obtained from a single puncture. In these patients, aged thirteen and three years and nine months, the differential diagnosis lay between aleukemic leukemia and hypoplastic anemia to explain the pancytopenia. In each case the bone marrow obtained from three sites — the sternum, the iliac crest and the spinous process — showed definite hypoplasia and no leukemic infiltration. In 1 patient further confirmation was obtained by trephine biopsy, which showed a hypoplastic marrow.

Discussion

There are definite advantages inherent in multiple sites for puncture. In such diseases as pernicious anemia, idiopathic thrombocytopenic purpura, multiple myeloma and leukemia, it is often desirable to obtain multiple punctures mainly for the purpose of following the course of the disease or the effects of therapy. When several punctures are performed, not only is the use of multiple sites more readily accepted by the patient but also, with the spinous-process approach, a *group* of possible sites for successive puncture is available. In one of our patients with pernicious anemia of pregnancy treated with folic acid, five successive spinous-process punctures were made at the seventh, eighth, ninth, tenth and twelfth vertebras, respectively. The patient reported very little discomfort, and an excellent opportunity was afforded to follow the changes in the marrow after therapy.

In patients in whom the diagnosis is in question and particularly when hypocellular marrow preparations are obtained, the use of multiple sites offers a means of confirmation of marrow diagnosis. A hypocellular marrow preparation obtained by sternal aspiration may leave one in doubt whether this represents a hypoplastic anemia or an inadequate sampling. The finding of hypocellular preparations in all three sites is a very definite indication that hypoplasia or fibrosis is actually present.

The use of alternate sites may provide information that is lacking if only the sternal marrow is examined. Just as biopsy of a lymph node or of the liver or spleen may throw additional light on a diagnostic problem, so, on occasion, spinous-process and iliac-crest punctures provide data that would otherwise be lacking. For example, in a recent case, the sternal and spinous-process punctures yielded normal marrow, but iliac-crest aspiration showed a well defined infiltration with lymphosarcoma cells, thus establishing the diagnosis.

Additional uses of alternate sites often occur, as when a sensitive patient refuses to have a second sternal puncture, when irradiation of the mediastinum has so affected the sternal marrow that interpretation of the findings of the sternal aspiration may be difficult or open to question, when the sternum is unusually tender to pressure (this occurs in a number of hematologic disorders) and, in certain cases of metastatic disorders, when localized bone pain or tenderness is present. By puncture of the bone in the region of the most marked tenderness, the possibility of finding carcinomatous cells is considerably enhanced.

Summary

In this laboratory, in which examination of the bone marrow is believed to be an integral part of hematologic study, the use of alternative sites for bone-marrow puncture has been found to be of definite value. In children, the spinous process and iliac crest are often the preferred site for puncture.

A series of cases is briefly presented to demonstrate the use and value of punctures at multiple sites.

References

1. Van den Berghe, L., and Blitstein, I. Advantages du prélèvement de la moelle osseuse par ponction de la crête iliaque. *Presse méd.* **53**:419, 1945.
2. Rubenstein, M. A. Iliac crest versus sternal bone marrow puncture: diagnostic importance. *J. A. M. A.* **134**:55, 1947.
3. Loge, J. P. Spinous process puncture. Simple clinical approach for obtaining bone marrow. *Blood* **3**:198-204, 1948.
4. Huss, J. H., Gilbert, J., and Liebow, A. A. Method for obtaining bone marrow by vertebral spinous process puncture. *Yale J. Biol. & Med.* **20**:291-297, 1948.

MEDICAL PROBLEMS OF OLD AGE*

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EIGHT years ago, a geriatric clinic was established in the Out-Door Department of the Peter Bent Brigham Hospital in Boston. Its purpose was to study old people from a fresh point of view in an academic atmosphere. It sought to define the medical problems imposed by age. Are diseases in old people different from the same diseases in younger ones? Are diagnostic problems altered by age? Can useful therapeutic measures and programs be devised? In short, is there a place for geriatrics as a distinct discipline in the medical arts and sciences? This paper is the first report of progress from the clinic.

The location of the clinic excluded attendance by old people of independent means, those too feeble to come, and those in almshouses and private homes for the aged. But there was opportunity to study a few of the first group in private practice and to get information on the rest by association with the Committee on the Care of the Aged of the Boston Council of Social Agencies. Patients who came, though of every kind and condition, proved to be most co-operative and willing to do their part in the explorations. The project has not grown in size, partly because it was curtailed during the war and partly because it has received no financial support except for a few small, unsolicited contributions in the last year. It is still limited to one worker. However, sufficient experience has been gained to show that geriatrics can develop into a real medical specialty and that it is most likely to be developed in clinics where the necessary skills and tools can be fashioned for use by physicians, social workers, nurses, physiotherapists and all who deal with aged persons.

Old age is peculiarly the field of chronic disease. Disabilities and deficits incurred earlier in life are brought along into old age, and new ones appear. Persistent and recurrent diseases, such as peptic ulcer, gallstones, hernia and arthritis, are found in greatest frequency in old age. High blood pressure is observed in the majority of men and women over sixty, and heart disease in some form and degree disables or kills more than 50 per cent of them. Malignant lesions reach their greatest incidence in the aged. These conditions will continue to prevail no matter how much progress is made in particular areas or how long the average span of life is extended. This accumulation of troubles and our inevitable defeat account for the unhappy view of the last third of life that has always been held by society at large, and for the sense of futility in attempting to cope with its complex situations that most physicians feel. To say, "at your age, what can you expect," absolves the physician from further effort and lets the aged patient conclude that it is all up to him.

The geriatrician holds, however, that this is not sound reasoning. These disabilities come slowly and in varying degrees, so that there is an opportunity for the patient to adjust himself to them, satisfactorily in most cases. It is also clear that even now physicians have enough skill to care for chronic diseases and cardiovascular limitations sufficiently effectively to permit life to be lived at reasonably tolerable levels. Neuropsychiatric disasters are not so unresponsive to treatment as they appear to be. Life ends for many old people as naturally as it began, with little distress, in the midst of full, forward-looking participation in society, with no period of custodial care or sitting on the side-line benches. The geriatrician believes that this happy ending can be achieved by many more.

DETECTION OF DISEASE

The detection of disease in old people is not hard. A thorough search is likely to be only too rewarding. Recognition of the factors that are really producing symptoms, however, many require much insight and geriatric experience. For example, a spinster who for fifty years had made her way as a milliner in a down-town store went to a hospital to seek relief from headaches. Her glasses seemed to be correct. She was found to have high blood pressure. Sclerotic arteries were seen in x-ray films of the skull. She was referred to the neurologic clinic, where the blood pressure, the sclerosis, the headaches and the worries added up to a diagnosis of cerebral arteriosclerosis. She was advised to give up her work, to stop worrying and to sleep on several pillows so that her head would not become congested. She became much worse and had to accept charity. She was referred to the geriatric clinic by her minister. There her headaches were considered to arise from spasm of the erector spinae and trapezius muscles produced by worry and the position of stretch on pillows, and the attacks of vertigo appeared to come from an active carotid sinus reflex. She was advised to sleep without any pillow and to dance, to limber up the neck and to lessen external tension upon the carotid arteries.

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It took several weeks for her to gather courage to carry out the treatment. When she did, her symptoms cleared up. It took much longer for her to get confidence enough to go back to work. Here one can say that the hypertension and arteriosclerosis were anatomic but not clinical facts.

Much that passes for senility turns out to be merely physical unfitness. This is true of much feebleness, frailty, unsteadiness on the feet, awkwardness, undue fatigue, shortness of breath and slow motion. Very few people carry the ideal of a vigorous state of health long after they have left school and its periods of compulsory exercise behind. They exercise as their jobs require or as their vacations or hobbies lead them. When they retire or are retired, inertia seizes them. As a general rule, men in their working years are more fond of keeping physically fit than women are, but after retirement women maintain themselves better because they adjust themselves more naturally to home life than men do. There is no gainsaying the common knowledge that after sixty there are losses in speed and in endurance. But the experience of the geriatric clinic is clear that much can be accomplished, mentally as well as physically, by simple games (bowling, shuffle board and ring toss) and by dancing to restore the sense of timing and coordination. The clinic patients have responded well when the only available outlet was their own ingenuity and the radio. It is also clear that regular exercise and play have beneficial effects on patients with high blood pressure, hypertensive heart disease, arthritis, emphysema, paralysis agitans and hemiplegia. Here is a field of rehabilitation as exciting and as rewarding as that with war casualties. A great deal is packed into the phrase of Juvenal: *mens sana in corpore sano.*

Much that appears to be mental deterioration in old age is not so at all. Perhaps not more than 10 to 15 per cent of old people show organic, irreversible losses of mental functions. Very few people study after their school days, except as their livelihood compels them. Their reading may be limited to newspaper headlines and magazines. When they lose their jobs, they often find themselves too rusty to activate unused aptitudes or restore neglected hobbies and studies, and they drift along idly on daydreams. Or an accident, loss of sight or hearing or locomotion, loss of family or friends or fortune, loss of accustomed reasons for living finds them so concentrated on their misfortunes that they have no attention to give to things that go on around them. Therefore, these things are not remembered, and, since loss of memory is a sign of old age, they are thrust deeper in depression by being made aware of that fact. They depend upon others to remember things or to do tasks that the limitations of old age prohibit, and dependency paralyzes their intellectual output still more. Certain diseases produce flagrant states of psychoses, which clear up when they are cured or controlled — for example, severe anemia, high fever, severe heart failure and obstructive situations in the urinary tract. The geriatrician is conscious of how important it is for the mental health of his patient that he treat vigorously every interfering ailment and find ways of restoring confident living.

It is appropriate that the old person's chief complaint may have little to do with what really concerns him. Even if it does, there are other complaints and many matters that he needs to talk over with someone. He has outlived the parents to whom he turned in time of trouble. His friends are gone, and now, still the same human being, in the dark about how to pursue his course, or how to find a course to pursue, he must bring himself to turn for advice to younger people; it is equally difficult for younger people to give him an attentive ear — for the pupil to turn teacher. Who is in a better position to give friendly, neutral, skillful, understanding advice than the medical adviser? Here is a tremendous extension of medical responsibility far beyond what can be taught in school or laboratory. But the old-fashioned general practitioner fulfilled this responsibility. It is a burden that practitioners today must recognize and assume if they are to deal adequately with the needs of old people. It takes an endless amount of time, much insight and ingenuity, tolerance and patience. The reward is in making the last third of life worth while to many persons.

A typical problem in geriatrics is illustrated by the first patient referred to the clinic. She was a sixty-eight-year-old Austrian widow who complained of belching of gas and epigastric burning. She had been studied by every medical house officer in the Peter Bent Brigham Hospital in the course of the previous five years; four gastrointestinal series, two barium enemas and two x-ray examinations of the gall bladder were negative; all therapeutic reassurance and diets and medications were of no avail. She sat across a narrow table from the examiner and for an hour and a half described and illustrated her symptoms. Her appearance was not prepossessing, for the motion of her false teeth did not synchronize with the tremor of her head. The examiner, determined not to abandon geriatrics at the first shot, asked questions from time to time — who she was, where she came from, how she lived. Finally, she began to answer them, and for ten minutes she gave a detailed story of her origin and emigration to America, where she stayed first, where she worked, how she met and married her husband, how he had died and how she had subsequently lived. She was asked to return in a week to discuss ways of spending her welfare allowance to better advantage, and it was then pointed out to her that she had not belched in the last ten minutes. "Oh," she said, "that doesn't bother me." And then it dawned upon the examiner that her nervous indi-

gestion was this poor, lonely, dependent woman's only claim to importance. She had no excuse for leaving her tenement except to go to church, to the store and to the hospital, where all the specialists were so interested in her. In subsequent visits her habits of living were reviewed, and a girlhood interest in Austrian cross-stitching was revived. At Christmas she exhibited samples of her art in the local saloon, which was the only place in the neighborhood with lighted windows. She continued to need welfare assistance, but no longer complained of gas or burning.

A generalization that time has strengthened was made early in the geriatric clinic: malnutrition and physical and mental unfitness are present in some degree in almost every person over sixty years of age. Malnutrition sets in with lack of a proper diet, as often from wrong ideas about food as from inability to get it. It can come from poor dentures or none. It can result from anorexia due to sorrow or loneliness or loss of drive. It can be intensified by disease, especially diseases with fever, blood loss or cachexia. There is often the hint that the aged organism needs more of certain food factors, such as vitamin B and vitamin C, than have been considered normal amounts for adults, whether from lack of absorption or lack of utilization. Components of the vitamin B complex now constitute the first thought in the clinic for old people with cramps in the legs at night or with unexplained depressions. The war made us conscious of the extra need for protein in cachexia, in hepatitis and in demineralization of bone. Fortunately, an adequate diet is available to all old people in this country — even to those receiving public or private assistance. It is very difficult to get those to take it who cannot change their habits or make substitutions or find value in being well. But the results are worth all the required patience and humor and ingenuity and preaching.

Effect of Drugs

A great deal of careful observation must be done before it is known whether and to what degree age alters the dosage and actions of drugs. There is an impression that the saturation and maintenance doses of digitalis, for example, are smaller in old persons than in the young or middle-aged. A high concentration of sulfadiazine in the blood is reached rather quickly on small doses, probably because renal filtration is not as efficient in old age. When morphine is administered one should remember the sensitiveness of the respiratory center. Sedatives should be given with much caution, for bromides tend to produce psychotic states and the barbiturates appear to leave the body slowly. The custom of giving small daily doses of phenobarbital to control nervousness and small nightly doses of some other barbiturate to promote sleep is condemned. By their depressive action the drugs increase the fear of loss of mental competence, and by their accumulative tendency they soon fail to produce a satisfactory period of unconsciousness. These objections do not appear to apply to the salicylates or alcohol.

General Therapy

The tools that the geriatrician needs are community projects of many kinds. Old-age clubs where lonely, idle persons can go daily for association, for games, for reading, for dances and for developing hobbies are needed. Several are now in existence in Boston. They are not very expensive, but they demand good leadership to control the cantankerous and to bring out the leaners. The natural places for the many more that are needed are the public schools, which are close to old people in every neighborhood, which are for the most part idle in late afternoons and evenings, and which could become truly community centers. Vacation projects are helpful, for elderly persons need the revivifying effects of a change of scene fully as much as young ones, whether or not they are working. Old people on charity seldom get a chance to leave their meager quarters. Most of those who are independently situated live on too narrow a budget to permit a reasonable stay at an attractive place. The management of a farm here, a boardinghouse by the sea there and a camp by a lake somewhere else would be expensive, even if fees were levied according to means. But the benefits derived would be good therapy. And, since most old people would remain at home, there should be summer day-camp club projects in the city, preferably on a portion of public playgrounds, and under supervision to stimulate participation. An employment service, to define and produce paying situations that are suitable for old people and not unfair to young employees, is needed. There should be experiments in boardinghouses, supervised apartments with part-time housekeeping service, simple nursing homes and the activation of homes for the aged, to become homes in the full sense of the word and not merely places for custodial care. Best and most expensive of all is an old-age center where all these activities could be housed, directed and promoted; where there could be a gymnasium and swimming pool for rehabilitation; where there could be varied experiments with re-education toward hobbies or jobs or community service; where there could be a psychologic counseling service to determine the aptitudes and mental maturity level as objectively as possible; and where rich and poor could go to find ways to make their last years mean something.

Conclusion

The point of view of the geriatric clinic can be summarized thus. There are two groups of old people. There are the very old, those with such

limitations of body, mind and pocketbook that they need custodial care; these are the ones on whom most attention has been centered and the ones we have in mind when old age is thought of with dismay. But there are also young old people, most of them independent or at work. We must direct our efforts at them. If we do; if we discover means of keeping them at work, if we find ways for them to rehabilitate themselves physically and intellectually, if they are given adequate care in sickness and convalescence, and if they have normal opportunities for play, vacations, social association and community participation and for living, many of them will retain their independence, and the break to custodial care will be of short duration or will not come at all.

270 Commonwealth Avenue

CLINICAL NOTE

CONSERVATIVE TREATMENT IN PLACENTA ACCRETA

Report of a Case in Twin Pregnancy

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THE abnormal adherence of all or part of the placenta to the uterine wall, so-called placenta accreta, is a complication in obstetric practice that calls for accurate, rapid diagnosis, and perhaps emergency treatment. It is not a common finding; Irving and Hertig[1] record the incidence at the Boston Lying-in Hospital to be 1 in 1956 deliveries. The survey by Phaneuf[2] reveals a frequency of 1 placenta accreta in 14,622 deliveries. There is only one previous report of placenta accreta occurring in twin pregnancies.[3]

The dangers of hemorrhage and sepsis in adherent placentas have made immediate hysterectomy the accepted treatment. However, conservative therapy may have a definite place, especially when there is complete absence of uterine bleeding. In the following case of placenta accreta in twin pregnancy the patient was treated without surgical intervention:

Mrs. M. P., a 27-year-old primigravida, whose last menstrual period had begun on July 12, 1947, was admitted to the Malden Hospital on March 21, 1948, in premature labor. Pregnancy up to that time had been normal. The patient was Rh+. Under low spinal anesthesia, a living premature female infant was delivered by Scanzoni maneuver, after a right mediolateral episiotomy. Immediately after the birth of the infant, a large placenta with membranes and cord was delivered intact. At this time, it was noted that the uterus was still large, and within a few moments, a macerated stillborn female fetus was delivered along with an umbilical cord about 30 cm. in length broken off at its distal end. A second placenta and membranes did not present.

The first placenta was examined very carefully, and no place could be found where the second umbilical cord might have been attached. There was no sign of hemorrhage. After 45 minutes, the uterus was entered in an attempt at manual extraction of the second placenta, but no line of cleavage could be felt. A second obstetrician, called in consultation, was also unable to find a line of cleavage but did remove a few shreds of membrane. There was still no bleeding, and the patient's condition was good despite manipulation. The blood pressure was 120/70, the pulse 84, and the respirations 20. The flow were normal. Since the fundus was hard, firm and well contracted, all operative intervention was discontinued, and the patient was returned to her bed. On the following morning, the placenta had not been expelled. The patient was not bleeding and her blood pressure, pulse and temperature were normal. Penicillin was administered in a dosage of 100,000 units every 3 hours for 4 days. It was decided to observe her progress for at least 36 hours before considering surgery since there was no apparent indication for hysterectomy. At the end of this period, the patient was in excellent condition. The flow was not excessive, and the uterus was contracted and firm. A final decision against removal of the uterus was made. The patient was discharged 10 days after delivery, after an uneventful convalescence. Post-partum examination 6 weeks later revealed a well healed perineum and a normal fundus. She had a normal menstrual period 8 weeks after delivery.

In this case the question of a placenta succenturiata was considered as well as that of accreta, but pathological examination of the placenta revealed no site where the umbilical cord might have been inserted.

Nearly all writers agree that the treatment of placenta accreta is immediate hysterectomy. However, Schumann[4] cites special indications for conservative treatment and presents a series of 14 cases with no mortality and 2 subsequent pregnancies. His chief indication for conservative treatment is absence of bleeding.

In considering the fate of the placenta that was not expelled, one must hypothesize that since the fetus was stillborn and the first placenta was very large, the second placenta must have been very small and that, because of its small size, it did not have a sufficient blood supply and therefore degenerated. Secondly, this might have been an increta or percreta type of placenta (Kaltreider classification), which had so grown into the uterine musculature that it could not be removed.

This case was similar to those reported by Schumann.

Summary

A case of placenta accreta occurring in a twin pregnancy with one live infant and one macerated fetus is presented. The patient was treated conservatively and made an uneventful recovery.

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References

1. Irving, F. C., and Hertig, A. T. Study of placenta accreta. *Surg., Gynec. & Obst.* **64**:178-200, 1937.
2. Phaneuf, L. E. Placenta accreta: review of literature and report of two personal cases. *Surg., Gynec. & Obst.* **57**:343-351, 1933.
3. Picolli. Cited by Irving and Hertig.[1]
4. Schumann, E. A. Pathology of third stage of labor, with especial reference to placental element. *M. Rec.* **151**:381-384, 1940.

Additional References

DeLee, J. B., and Greenhill, J. P. *The Principles and Practice of Obstetrics.* Ninth edition. 1011 pp. Philadelphia: W. B. Saunders Company, 1947. Pp. 708 and 709.

Jarcho, S. Delivery of adherent placenta: report of three cases in which Mojon-Gabaston method was employed. *Surg., Gynec. & Obst.* **46**:265-272, 1928.

MEDICAL PROGRESS

CARE OF THE NEWBORN*

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FOR many years neonatal mortality rates resisted all efforts at reduction. In Massachusetts from 1910 to 1930 the infant mortality occurring from two weeks of age to one year fell over 60 per cent while the neonatal death rate fell but 14 per cent (Fig. 1). However, during the past fifteen years there has been a gratifying fall of 32 per cent in neonatal mortality, from a rate of 31 deaths per 1000 live births to a rate of 21. Despite this improvement the first two weeks still remains the most dangerous period in life — 64 per cent of the present infant mortality in the Commonwealth occurs during that interval.

A number of factors have contributed to the recent reduction in neonatal mortality. All people have enjoyed a higher standard of living, with resulting improved nutrition in the child-bearing group and the ability to command better medical care. There have been great advances in the sciences of obstetrics, pediatrics and public health and wide dissemination of this knowledge to the medical profession and general public. The federal Government, through the Children's Bureau, has paid particular attention to the welfare of the newborn, and much of the present success can be traced to these efforts. The district and local health departments have been very active in promoting programs to improve the care of the newborn, with splendid results. Not the least of the factors contributing to the improved status of the newborn has been the rapid shift of the scene of childbirth from the home to the hospital. In Massachusetts during the past year 96 per cent of all births took place in hospitals. While the over-all picture has improved, the shift from the home to the hospital has not been an unmixed blessing but has of itself created new problems, which are considered below.

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Prenatal Prophylaxis

The health and nutrition of the mother from the time of conception on may exert a direct influence on the developing embryo and fetus. The classic animal experiments of Warkany[1-3] have demonstrated that maternal diets completely deficient in vitamin A, B or D during the breeding period and the following fourteen days will produce a high incidence of malformation in the young, each vitamin lack producing a different and characteristic type of abnormality. These findings on animals must be applied to the problems of human nutrition with caution since no diet for human beings could be deprived of vitamins to the extent necessary to produce abnormalities in rats. Burke and his associates[4] analyzed the diets of 216 women observed throughout pregnancy and found in the 36 women on poor diets 8 infants with congenital anomalies whereas but 1 occurred in the group of 31 mothers on good diets.

Infection due to the rubella virus,[5] occurring early in pregnancy, has been found to cause congenital malformations in the newborn such as congenital cataracts and heart disease, deaf mutism, mongolian idiocy, microcephaly, hydrocephaly and mental retardation. Ingalls[6] believes that mongolism may be the result of injury to the embryo between the sixth and ninth weeks of life. He contends that agents responsible for this injury may include hemorrhage, threatened abortion, pathologic abnormalities of the uterus and certain acute infections. He suggests that these agents injure the embryo through anoxia, through temporary starvation or through the accumulation of toxic metabolites.

Ingalls states that forty years ago Mall stressed the importance of faulty implantation of a normal ovum in the production of a pathologic embryo and that, at the same time, Stockard concluded that two main mechanisms were involved in ab-

normal development. In one the abnormality was of germinal origin, producing accidents such as albinism, certain legless conditions and polydactyly. In the other, true monsters arose from normal ova developing under abnormal conditions or under unusual circumstances.

A number of studies have been made on the influence of prenatal factors on prematurity. Ebbs, Tisdall and Scott[7] found the incidence of miscarriages, premature births and stillbirths to be greater in a group of women on poor diets. Burke et al.[8] reported that the occurrence of stillborn, premature and functionally immature infants, as well as those with marked congenital defects, was practically limited to a group of mothers whose diet during pregnancy had been inadequate.

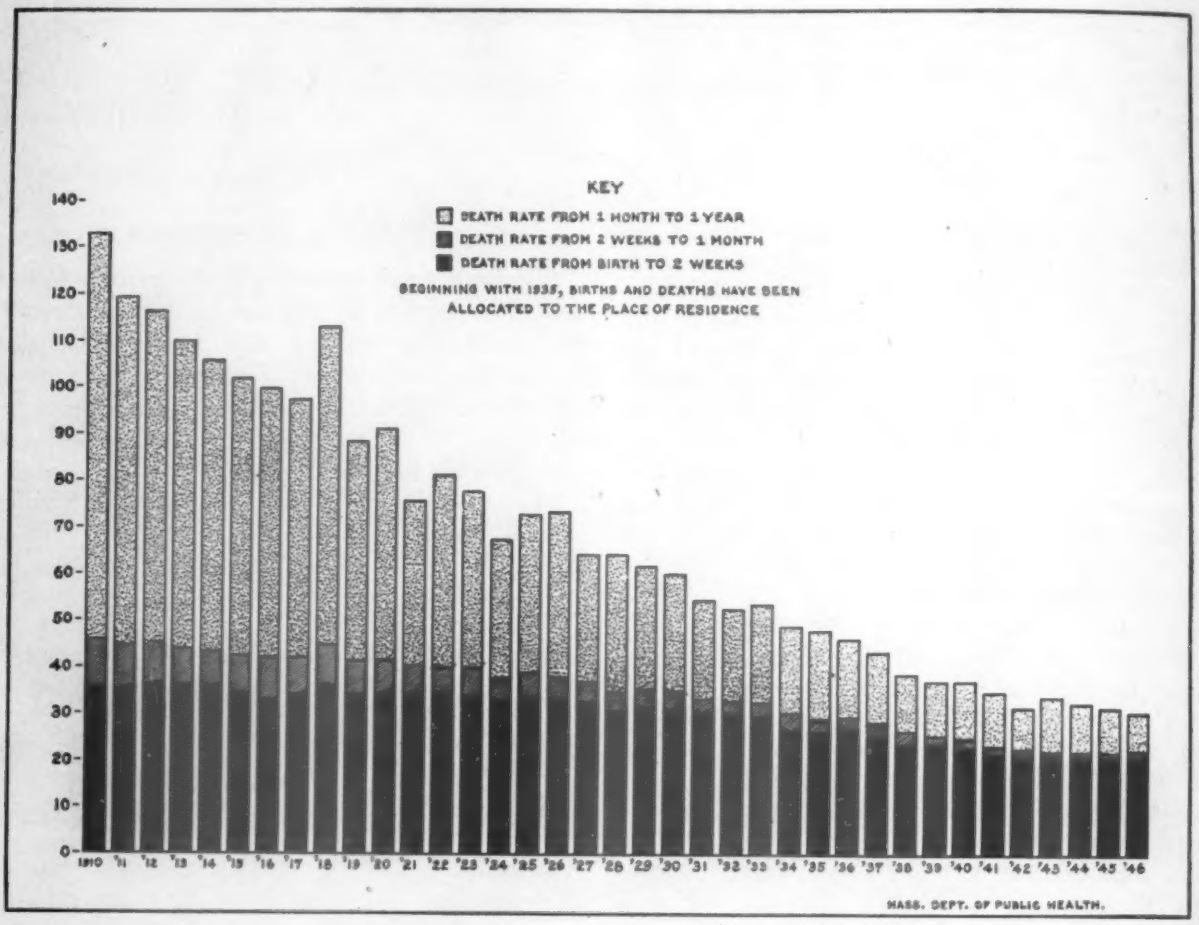
Brown, Lyon and Anderson[9] found the incidence of prematurity significantly increased by maternal illness, severe toxemia, eclampsia, mild bleeding, placenta previa, premature separation of the placenta, acute infections and chronic disorders of pregnancy.

It is thus apparent that many of the problems encountered in the newborn may be the aftermath of prenatal influences. Studies in this new field of prenatal prophylaxis should bring rich rewards both in reducing the incidence of stillbirths, premature births and congenital abnormalities and in improving the health of the newborn infant at birth.

Natal Prophylaxis

The present methods of safeguarding the baby during delivery represent one of the greatest achievements of modern obstetrics. The major dangers from which the infant must be protected result from trauma and anoxia.

Serious traumatic injury to the infant during delivery is now practically never seen. One important milestone in the elimination of traumatic injury was the substitution of physiologically sound pressure from above for traction from below. Almost overnight brachial palsies and spinal-cord transections disappeared and gross intracranial hemorrhages became exceedingly rare. Another important step was maternal analgesia that was safe for baby as well as mother. Because of the analgesia the mother was allowed to proceed through labor without inter-


KEY
DEATH RATE FROM 1 MONTH TO 1 YEAR
DEATH RATE FROM 2 WEEKS TO 1 MONTH
DEATH RATE FROM BIRTH TO 2 WEEKS
BEGINNING WITH 1935, BIRTHS AND DEATHS HAVE BEEN ALLOCATED TO THE PLACE OF RESIDENCE
140
130
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1910 '11 '12 '13 '14 '15 '16 '17 '18 '19 '20 '21 '22 '23 '24 '25 '26 '27 '28 '29 '30 '31 '32 '33 '34 '35 '36 '37 '38 '39 '40 '41 '42 '43 '44 '45 '46
MASS. DEPT. OF PUBLIC HEALTH.

Figure 1. *Infant Mortality in Massachusetts by Age Groups per 1000 Live Births.*

ference, and the incidence of high-forceps and mid-forceps extractions also practically disappeared. The third important milestone in the elimination of traumatic injury was the introduction of x-ray pelvimetry and the following of the progress of doubtful cases by serial x-ray examination. It is possible, but not proved, that the administration of vitamin K to the mother during labor has reduced the incidence of intracranial bleeding.

Protection of the infant from the devastating effects of anoxia is one of the major problems with which obstetricians are confronted today. In this clinic 58 per cent of the deaths among infants, both full term and premature, are the result of anoxia. There are, to be sure, many complications of pregnancy in which serious anoxia is unavoidable and beyond present methods of control. However, some types of anoxia are completely preventable. The use of high concentrations of nitrous oxide or of cyclopropane during labor will inevitably produce severe fetal anoxia. The practice of delaying delivery of the head by direct or indirect pressure to the perineum with or without deep maternal anesthesia is indefensible and extremely dangerous. It is frequently a tragedy that the baby involved in such a procedure survives but with gross neurologic damage.

Neonatal Prophylaxis

Hospitals have assumed a tremendous responsibility in attempting to provide care for all the newborn infants in the nation. The considerable confusion that surrounds the problem is due to a number of factors: the speed at which the shift from home to hospital took place; the shortage of hospital and nursery beds; the increased birth rate; the demand for care by a private physician and for private and semiprivate rather than ward accommodations; the shortage of nursing personnel; the problem of increasing costs and unbalanced budgets; and the unco-ordinated attempts by the overlapping interested groups of doctors, nurses, administrators and public-health authorities to offer independent solutions for the problem.

The position of the public-health authorities toward the care of the newborn in hospitals is clear. They must represent and protect the interests of the general public by establishing, after consultation with all interested groups, minimum standards and regulations for the hospital care of newborn infants as a basis for the yearly licensing of such obstetric units. They must make sufficiently frequent personal inspections to satisfy themselves that these minimum requirements are being continuously met.

The hospitals themselves should not be content with minimum standards but should strive at all times toward ideal care for their babies. The Committee on Fetus and Newborn of the American Academy of Pediatrics has committees on fetus and newborn organized in forty-seven states, four Canadian provinces and Hawaii, and each committee is anxious to co-operate with any hospital group in helping to solve its individual nursery problems.

Any hospital seeking to organize and improve its newborn service can obtain valuable assistance from the Manual, *Standards and Recommendations for Hospital Care of Newborn Infants — Full Term and Premature*, prepared by the Committee on Fetus and Newborn of the American Academy of Pediatrics and now in press.

Diseases of the Newborn

The major causes of morbidity and mortality in newborn infants, full term and premature, are relatively few — anoxic injuries, traumatic injuries, infections, congenital defects and erythroblastosis. It is of great practical importance that the vast majority of these conditions can be recognized within the first forty-eight hours of life. It would be highly desirable, therefore, if all newborn infants could be closely observed and examined by specially trained nurses and pediatricians, if possible in a special nursery, for the first twenty-four to forty-eight hours of life, before being distributed to their regular nurseries.

By all standards the most important cause of newborn morbidity and mortality is anoxic injury, which alone accounts for nearly 60 per cent of mortality. Anoxia[10] produces progressively congestion, edema, hemorrhage and necrosis in any or every organ and tissue of the body. The combinations of clinical symptoms that may result are almost unlimited. The only treatment that will stop the cycle of anoxic injury is the administration of oxygen. Many newborn infants are immediately placed in an atmosphere of 50 to 60 per cent oxygen as a prophylactic measure even before clinical symptoms have become evident. Undoubtedly, more oxygen than is necessary is used, but it is believed that this procedure has prevented the occurrence or minimized the extent of dangerous complications in an unknown number of infants. All prematurely born infants are routinely placed in an oxygen bed for at least twenty-four hours, and all those with erythroblastosis severe enough to require treatment, and all those with atelectasis are kept in oxygen for four or five days. All babies with a history of fetal distress and all who have required resuscitation are automatically placed in oxygen.

The generalized edema that develops in both full-term and premature infants as the result of anoxia is a very striking finding. It may be a fatal error to start giving fluids too early to such infants in the presence of edema. The added fluid increases the existing edema and may produce serious cerebral and pulmonary complications. It is a fixed policy to give no fluid to premature or full-term infants in the presence of edema. In rare cases

a small premature infant may receive nothing for as long as four or five days. This principle of managing edema was postulated on clinical grounds and has been associated with a further lowering of premature infant mortality to 16 per cent. The work of Smith[11] has now given chemical support to this thesis.

Infants with intracranial bleeding,[12] whether due to anoxia or trauma or both, are kept in oxygen, given nothing by mouth for several days and treated by repeated lumbar punctures until the spinal fluid is practically normal.

The birth of erythroblastotic infants may be forecast weeks before term by the appearance of anti-Rh agglutinins in the serum of mothers with a suggestive history and Rh setup. When it is obstetrically advisable these babies are delivered several weeks before maturity. Blood from the infant's umbilical cord is immediately studied for Rh type and the presence of Rh antibodies. If circulating antibodies are demonstrated the infant receives an immediate replacement transfusion with Rh negative blood. Under this routine the mortality from erythroblastosis has fallen from 40 to 10 per cent.[13] Unfortunately, the incidence of kernicterus has not been reduced by present methods of treatment.

Pediatricians have an increasing obligation to recognize certain congenital defects early in the newborn period since an increasing number can be cured by prompt surgical procedures. Only a few years ago all babies with a tracheoesophageal fistula died — today 8 out of 10 should be completely repaired.[14] Every infant exhibiting an unusual amount of oral mucus immediately after birth should be suspected of having this condition until the contrary is proved. The diagnosis is made by the demonstration of a blind esophageal pouch through the passing of a stiff catheter into the esophagus and the taking of an x-ray film with the catheter in place.

One in every 4 infants with congenital absence of the bile ducts has a condition that may be cured by surgical intervention.[15] It must be remembered that jaundice may be very slight in this condition throughout the newborn period. Every case of even mild jaundice must be considered as a potential congenital obliteration of the bile ducts until proved to the contrary.

Congenital obstruction of the intestine is a relatively common condition in the newborn — including premature infants. Every case of vomiting in the newborn, especially if it begins immediately after birth, must be considered obstruction until disproved. The obstruction may be intrinsic and, if multiple, may be inoperable. It may be due to meconium ileus and require operation or to a meconium plug in the rectum or descending colon and respond dramatically to a simple enema. It may be caused by constriction by short bands of mesentery associated with malrotation of the cecum or by a volvulus, intussusception, pyloric stenosis or diaphragmatic hernia. A 3-pound premature infant with an obstruction due to an annular pancreas was successfully operated upon on the sixth day of life. The common symptom of obstructions is vomiting, and the diagnosis can frequently be made by a plain x-ray film of the abdomen.

Infection

It should never be forgotten that both premature and full-term infants may develop all the types of infection seen in older infants. They are particularly susceptible to infections that may enter through the umbilical vessels. However, at present I am particularly concerned with a relatively new type of infection that has appeared secondary to the concentration of large numbers of babies in common nurseries. Epidemic diarrhea of the newborn has become a public-health problem only during the past fifteen years.

A review of the literature on this condition[16] warrants the conclusion that it is not a pathologic entity but rather a symptom complex that may be caused by a variety of organisms and by at least one and possibly more viruses. The conclusion was reached that many epidemics were caused by glaring errors in nursery technic and by faulty epidemiologic management of the first cases of diarrhea that appeared. It was suggested that simple sound nursery practice could prevent practically every epidemic of diarrhea even in crowded nurseries.

The New York State Public Health Council on January 16, 1948, added a new regulation to its sanitary code designed to control diarrheal diseases of the newborn in nurseries.[17] These regulations were arrived at after consultation with the New York State Medical Society, many individuals and organizations and were written to agree in principle with the recommendations of the Children's Bureau and the Committee on Fetus and Newborn of the American Academy of Pediatrics. The New York Department of Health summarizes the requirements of Regulation 35 as follows: mandatory terminal "sterilization" of formulas in individual feeding bottles with nipple and nipple cap attached, certain principles of isolation, the use of the "suspect" nursery systems for observing infants with suspicious signs of illness, individual care for each infant with his own equipment, adequate space for such care, adequate nursing personnel, smaller groups of infants in each nursery and careful handwashing by physicians and nurses after coming in contact with any infant.

A similar program was proposed, but not made mandatory, by the Massachusetts Department of Public Health at a series of conferences throughout the Commonwealth in June, 1947. Dr. Roy F.

Feemster, director of the Division of Communicable Diseases, has given me permission to report the amazing sequel of these conferences. In the period from June, 1946, to June, 1947, the Department of Public Health was forced to close the newborn nurseries of 9 maternity hospitals because of outbreaks of epidemic diarrhea. All these outbreaks were serious, with fatal cases in each. From June, 1947, to April, 1948, there was not a single epidemic of newborn diarrhea in the Commonwealth. The Department was called in by 11 hospitals with isolated cases of newborn diarrhea; no nursery was closed, and no deaths occurred in any of the reported cases.

Care of the Premature Infant

Care of the prematurely born infant is the major problem of the neonatal period. Every hospital can anticipate that 5 or 6 per cent of their expected births will be infants weighing 2500 gm. (5 pounds and 8 ounces) or less and that from this small group will come 60 per cent of the newborn mortality.

The Children's Bureau[17] has been a leader in efforts to improve the care of premature infants and is ever ready to assist state and local groups in their problems. Since 1935 the Bureau has had the responsibility of administering grants-in-aid to states for maternal and child health under the Social Security Act. The maternal-health and child-health fund available for state grants amounts to $11,000,000 per year, half of which goes to states in proportion to their number of live births and must be matched dollar for dollar from state funds. To receive its share a state must submit a plan outlining its proposed program and indicating how it will meet certain requirements of the act. Forty-four states have some activity in relation to premature infants financed from maternal-health and child-health funds. At present 7 states have premature centers now in operation, and 6 more states are in the process of starting such centers. Most of the states concentrate on one, two or three good centers to which premature infants are brought by ambulance.

The details of organizing, equipping and operating a nursery for premature infants are beyond the limits of this discussion and may be found in *Care of Premature Infants*, published by the Division of Maternal and Child Hygiene, Illinois Department of Public Health; in the *Recommended Standards for the Care of Premature Infants*, of the Bureau of Child Hygiene, New York City Department of Health; and in the manual mentioned above that is to be published by the Committee on Fetus and Newborn of the American Academy of Pediatrics.

Methods to protect the premature infant from infection deserve some consideration. If it is granted that for practical purposes all premature infants at the moment of birth are free from infection, it is a striking fact that in some nurseries infection of premature infants, usually accompanied by diarrhea, is virtually unknown, whereas in other nurseries it is a constant major problem. It is my strong conviction from years of experience with the problem that premature infants born in a hospital devoted exclusively to obstetrics, where the medical and nursing staff have no contact with infected general-hospital patients and no contact with other doctors and nurses caring for such patients, are peculiarly free from infection, with or without diarrhea. Premature infants born in the obstetric ward of a general hospital, even when cared for in a separate nursery, are prone to infection and diarrhea. Premature infants transported to a premature nursery setup in connection with a general pediatric hospital are particularly susceptible to infection and diarrhea. In my own experience the incidence of infection and diarrhea has been sharply curtailed — but not eliminated — in a premature nursery operated as part of a general infants' hospital when each premature infant is kept strictly isolated in a Chapple bed.

As a result of the above experience I recommend that premature centers be located in obstetric hospitals; in an independent building widely separated from a general hospital with a completely independent staff; if in connection with a general hospital — as far away from the children's and infants' wards as physically possible and equipped so that each infant can be kept and cared for in its own air-conditioned unit throughout its entire stay.

Cultivation of a Normal Mother-Infant Relation

McLendon[18] has summarized the cultivation of a normal mother-infant relation as presuming breast feeding; observation by the mother of her newborn child's development; partial care of her newborn infant commensurate with her physical ability; the consequent accumulation of knowledge of her infant's behavior characteristics, particularly in connection with hunger; and confidence in her ability to interpret behavior expressions and to handle them properly.

Macneill[19] points out that the *place* of birth has a definite relation to breast feeding. In Detroit the incidence of breast-fed babies varied from 5 to 6 per cent in one hospital to 69 per cent in another. In Philadelphia a survey in two hospitals revealed a ratio of 24.6 per cent to 83.3 per cent. Common experience indicates that such discrepancies between hospitals exist.

Aldrich[20] has summarized the advantages of breast milk as a specific food and the advantages of breast feeding as a technic in child care. In connection with breast feeding he points out that teachers and laymen interested in the emotional problem of children, psychologists, psychiatrists and pedi-

atricians interested in growth and development all emphasize that this form of feeding provides a greater feeling of security to the baby. Through nursing at the breast the baby may gain a feeling of physical continuity with his mother, which as he progresses may lead to the feeling of "belongingness" considered by many psychiatrists to be the first step in the normal mother-child relation. The mother herself may benefit physiologically and psychologically through thus demonstrating her real importance to the infant.

The mother must be "sold" on the idea of wanting to nurse her infant — if possible, during the prenatal period. Many obstetricians begin this process of education at the first prenatal visit. Everyone knows how futile it is to try to convince a young mother that she should nurse her baby if her mind has been made up to the contrary. Aldrich[20] states that many psychiatrists consider that if a mother actively rejects the idea of nursing, it is probably unwise to urge it.

The obstetric department, psychiatric consultant and nursing school are experimenting with prenatal clinics on the psychologic preparation of the patient for childbirth in which the importance of future breast feeding is not neglected. It is too early to quote results, but the number of infants completely breast fed on discharge has risen to above 50 per cent.

Real help is needed for reducing the number of breast-feeding failures in willing mothers. Macneill[19] gives an excellent consideration of this problem. He considers some cracked nipples to be caused by the infant's efforts to obtain milk from an obstructed channel, the obstruction persisting unless the tension within the breast is lessened. When the secreting cuboidal cells become flattened by milk pressure, milk production stops. Waller[21] has shown that the careful and judicious use of stilbestrol in the early stages of increased milk tension relieves the pressure and inhibits the onset of the edema, which becomes the obstructing factor. Waller also claims that the prenatal removal of colostrum through manual expression, by the instructed expectant mother, from about the seventh month of pregnancy on, will facilitate the passage of milk through the breasts and lessen the hazard of engorgement. Macneill[19] advises that injured nipples be treated by the early application of hypertonic compresses to painful nipples and the protection of the injured nipples by a soft, rubber, conforming breast shield until the injury is healed.

All recent authors agree that the "rooming-in" system of infant care and "demand feeding" will contribute materially to successful breast feeding as well as satisfy the other postulates McLendon[18] has laid down for the cultivation of a normal mother-child relation.

A four-bed "rooming-in" unit has been in successful operation at the New Haven Hospital[22] for over a year. Montgomery[23] has used the "rooming-in" system for a number of his private patients in single rooms, with excellent results. In both these groups the mothers were highly selected.

In the private wing of the Boston Lying-in Hospital the "rooming-in" system has been available to mothers scheduled for single rooms for over a year. To date 20 patients have elected this service with but 1 failure. There were nearly 3000 births on the private service during this period, which does not indicate a very great demand. However, more interest in the proposition is evident at present, owing to wide publicity and accelerating interest on the part of the obstetricians. I have no idea how large a proportion of the child-bearing population would elect this system if it were offered to them. Its growth, like that of breast feeding, will depend on prenatal preparation.

On the wards a modification of the "rooming-in" system along the lines of Barnett's[24] experience at Los Alamos is planned. It is proposed to keep the babies in the nursery at night but to have the bassinettes at the mothers' bedside for the entire day, except for the general visiting hours. So far as possible, the mothers will take complete charge of their babies under expert nursing supervision.

Summary and Conclusions

Modern care of the newborn is concerned with attention to factors that may operate before and during birth as well as in the neonatal period. The health and nutrition of the mother from conception on may affect the embryo and fetus and may be responsible for congenital malformations, abortions, stillbirths and premature births. The prenatal period offers the ideal opportunity to prepare the mother psychologically for the nursing and care of her baby.

The major causes of disease in the newborn are anoxic injuries, traumatic injuries, infections, congenital defects and erythroblastosis. Some anoxic injury can be arrested or minimized by improvements in obstetric technic and through the prophylactic use of oxygen. When the anoxic injury is accompanied by generalized edema the administration of fluid is contraindicated. The mortality due to erythroblastosis fetalis has fallen as the result of early delivery in indicated cases with immediate replacement transfusion. If diagnosed promptly, many patients with congenital malformations (such as tracheoesophageal fistulas, absence of the bile ducts, various types of intestinal obstruction and diaphragmatic hernias) now have an excellent chance of being cured by operation. There is good reason to believe that epidemic diarrhea of the newborn can be eliminated through improved nursery technic and the application of simple epidemiologic principles.

Prenatal prophylaxis may reduce the number of premature infants born. Standards and recom-

mendations are available to improve the care of these infants in premature nurseries. A major problem remains — the protection of the premature infant from infection during his nursery stay.

While the infant is in the hospital every effort should be made to lay the groundwork for a future sound mother-infant relation. The cultivation of this relation is helped by breast feeding and the adoption of some modification of the "rooming-in" principle.

References

1. Warkany, J., Nelson, R. C., and Schraffenberger, E. Congenital malformations induced in rats by maternal nutritional deficiency: use of varied diets and of different strains of rats. *Am. J. Dis. Child.* **64**:860-866, 1942.
2. Warkany, J. Effect of maternal rachitogenic diet on skeletal development of young rats. *Am. J. Dis. Child.* **66**:511-516, 1943.
3. Warkany, J., and Schraffenberger, E. Congenital malformations of eyes induced with maternal deficiency of vitamin A. *Am. J. Dis. Child.* **69**:330, 1945.
4. Burke, B. S., Beal, V. A., Kirkwood, S. B., and Stuart, H. C. Nutrition studies during pregnancy. *Am. J. Obst. & Gynec.* **46**:38-52, 1943.
5. Erickson, C. A. Rubella early in pregnancy causing congenital malformations of eyes and heart. *J. Pediat.* **25**:281-283, 1944.
6. Ingalls, T. H. Etiology of mongolism: epidemiologic and teratologic implications. *Am. J. Dis. Child.* **74**:147-165, 1947.
7. Ebbs, J. H., Tisdall, F. F., and Scott, W. A. Influence of prenatal diet on mother and child. *J. Nutrition* **22**:515-526, 1941.
8. Burke, B. S., Beal, V. A., Kirkwood, S. B., and Stuart, H. C. Influence of nutrition during pregnancy upon condition of infant at birth. *J. Nutrition* **26**:569-583, 1943.
9. Brown, E. W., Lyon, R. A., and Anderson, N. A. Causes of prematurity. IV. Influence of maternal illness on incidence of prematurity: employment of new criterion of prematurity for Negro race. *Am. J. Dis. Child.* **70**:314-317, 1945. VI. Influence of toxemia on incidence of prematurity. *Ibid.* **71**:378-386, 1946. VII. Influence of uterine bleeding on incidence of prematurity. *Ibid.* **71**:482-491, 1946. VIII. Influence of infections, chronic disorders and accidents on incidence of prematurity. *Ibid.* **72**:189-201, 1946.
10. Clifford, S. H. Effects of asphyxia on newborn infant. *J. Pediat.* **18**: 567-578, 1941.
11. Smith, C. A. Adjustment of electrolyte and water equilibrium of premature infant. *Am. J. Dis. Child.* (in press).
12. Clifford, S. H. Management of emergencies. *Am. J. Dis. Child.* **73**: 706-712, 1947.
13. Diamond, L. K. Personal communication.
14. Swenson, O. Diagnosis and treatment of atresia of esophagus and tracheo-esophageal fistula. *Pediatrics* **1**:195-204, 1948.
15. Gross, R. Personal communication.
16. Clifford, S. H. Diarrhea of newborn. *New Eng. J. Med.* **237**:969-976, 1947.
17. Bain, K. Functions of federal Government in protecting newborn and in developing and improving facilities for care of full-term and premature infants. *Pediatrics* **2**:98-101, 1948.
18. McLendon, P. A. Suggestions for "rooming-in" nursery. *Am. J. Dis. Child.* **74**:376, 1947.
19. Macneill, M. Can we retrieve breast feeding? *Pennsylvania M. J.* **51**: 137-140, 1947.
20. Aldrich, C. A. Advisability of breast feeding: survey of subcommittee of Committee on Maternal and Child Feeding, National Research Council. *J. A. M. A.* **135**:915, 1947.
21. Waller, H. Cited by Macneill.[19]
22. Jackson, E. B., Olmsted, R. W., Foord, A., Thoms, H., and Hyder, K. Hospital rooming-in unit for four newborn infants and their mothers. *Pediatrics* **1**:28-43, 1948.
23. Montgomery, J. Personal communication.
24. Barnett, H. L. Note on experiences with rooming-in arrangement for newborn infants in small hospital. *J. Pediat.* **31**:49-53, 1947.

Correction. On Page 918 of the paper "Diphtheritic Myocarditis" by Drs. Boyer and Weinstein, which appeared in the December 9 issue of the *Journal*, the last figure in the column headed "Mortality" in Table 6 should be changed from "78.0" to "89.0." On Page 919 of the same paper, in the second line of the summary, "normal" should be changed to read "abnormal."

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35021

PRESENTATION OF CASE

A fifty-seven-year-old man was admitted to the hospital after an x-ray study of the chest had revealed a recent infiltration in the right lower lobe.

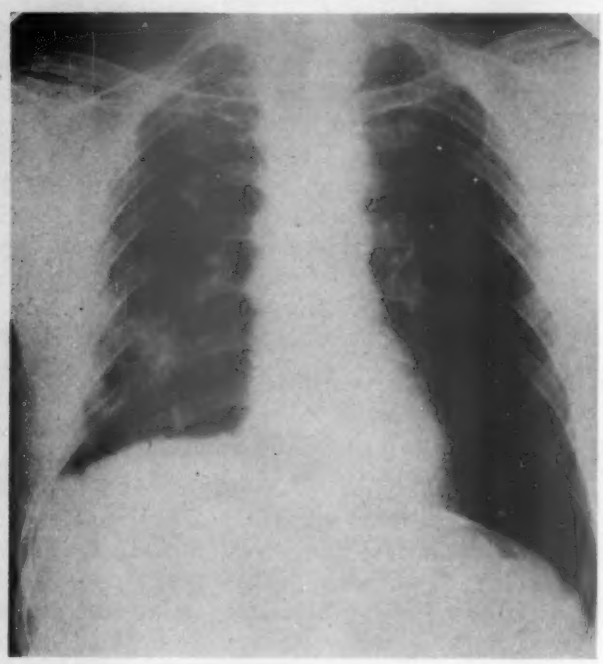

FIGURE 1.

The patient was in good health until three years before admission, when chills, fever, dyspnea and hemoptysis of 1 cupful of bright-red sputum appeared. He was given penicillin, and the respiratory symptoms rapidly cleared, but a sense of weakness persisted for several months. X-ray films during the illness showed "scars." The sputum was negative for tuberculosis. Two years before admission he developed a morning cough, productive of a cupful of mucoid sputum, and he became fatigued. Six months later a second hemoptysis occurred. An x-ray film showed "an apical fibrotic lesion on the right, and a diffuse infiltration at the right base with excavation." The sputum was positive for tubercle bacilli. Phrenic crush, solganal-B oleosum and bed rest for five months were employed. The sputum was positive for two months and then became negative and remained so. X-ray films seven months before admission showed no change in the lesion in the right base (Fig. 1). He regained the 25 pounds he had lost prior to hospitalization. He worked for several months but then had several small hemoptyses. X-ray films taken two months before admission showed some spread of the lesion,

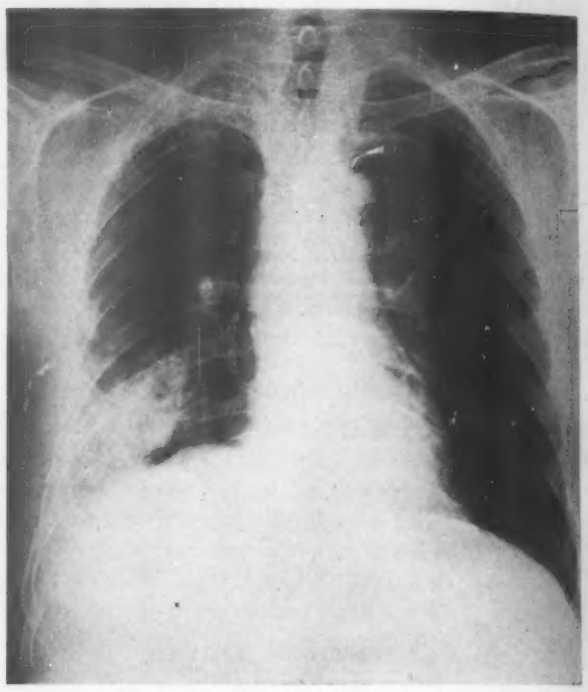

FIGURE 2.

which was now very pronounced in the right lower lobe. He was given streptomycin for two weeks, but this was discontinued because of nausea. Several chest taps two weeks before admission did not yield any fluid. There had been no recent anorexia, hoarseness, chest pain or weight loss.

Physical examination demonstrated increased breath sounds and tactile fremitus in the right upper posterior chest. Decreased breath sounds were present in the right base. Scattered rales were present in the right axilla. The remainder of the examination demonstrated no abnormalities. The blood pressure was 150 systolic, 85 diastolic.

Laboratory examination showed a normal urine, with a specific gravity of 1.024, a white-cell count of 9700, a hemoglobin of 14.6 gm. and a sedimentation rate of 4 mm. in 1 hour. Smears of the sputum were negative for acid-fast organisms.

Chest x-ray films showed irregular areas of increased density in both upper lobes, more marked

on the right. The trachea was displaced to the right side. At the right base posteriorly there was a relatively homogeneous area of increased density, measuring 8 cm. in its greatest dimension. There were several radiolucent zones identified in the upper portion of the density (Fig. 2). The right leaf of the diaphragm was elevated. There was no obvious obstruction to any of the major bronchi. Bronchoscopy demonstrated a cherry-red lesion in the posterolateral division of the right lower lobe. The patient bled about 70 cc. from the site of the biopsy, which on microscopical examination showed only blood clot.

An operation was performed on the seventh hospital day.

Differential Diagnosis

Dr. F. Dennette Adams: The history states that "phrenic crush, solganal-B oleosum and bed rest for five months were employed." I start by confronting this audience with a question and asking for a show of hands. How many know what solganal-B oleosum is?

Dr. Donald S. King: I know — since yesterday, that is. (Two other hands were raised.)

Dr. Adams: I first scoured the hospital, and then went to work on the telephone. Finally, while I clung to the receiver, Dr. King gave me the answer, but he looked it up. Is that correct, Dr. King?

Dr. King: Yes.

Dr. Adams: It is a gold preparation, which has been claimed to be very good for arthritis and diseases of the lupus group, except acute lupus, and is of doubtful value in tuberculosis. Dr. King tells me that certain groups on the continent are investigating the use of gold in tuberculosis.

Dr. Mallory, is there anything in the record about the percussion note of the lungs and fremitus elsewhere than in the upper portions? (I asked about the percussion note and fremitus because that information might help one decide whether he is dealing with solid tumor, fluid, localized empyema or collapse.)

Dr. Tracy B. Mallory: The percussion note is checked as being abnormal, but that is not explained or amplified.

Dr. Adams: Fremitus is not mentioned except in the right upper lobe?

Dr. Mallory: That is correct.

Dr. Adams: Where the sign is the least dependable. Did the patient run a fever during his hospital stay?

Dr. Mallory: The temperature was normal throughout, except for a day following the bronchoscopy, when it was 100°F.

Dr. Adams: The diagnosis must be largely based on the x-ray findings. One cannot make it on history or physical signs alone. The patient was sent into the hospital because of x-ray findings so we may as well see the films now.

In spite of the normal chest film three years before admission, one wonders if, at the start of the illness, the patient did not have lobar pneumonia that lighted up a latent tuberculosis. If the initial episode was tuberculosis, it is inconceivable that he could have been so acutely ill and recovered so rapidly. One could then further postulate that he developed empyema at that time, but absence of evidence of fluid in subsequent x-ray films seems to exclude this possibility. So we must start this problem with his second hemoptysis two years and six months following the first acute illness. Dr. Wyman, how far back do your films go?

Dr. Stanley M. Wyman: About seven months before entry to this hospital.

Dr. Adams: About the time of the second hemoptysis.

Dr. Wyman: These films begin seven months before entry to this hospital and show an infiltrative fibrotic area in the right-upper-lung field, with a small amount of similar infiltration on the left. The trachea is displaced toward the right. The right leaf of the diaphragm is slightly elevated in position, possibly owing to the phrenic crush described. There is an ill defined, round shadow of density in the right-lower-lung field. Four months later there is a suggestion of a large area of rarefaction in the center of the lesion, which may have increased slightly in density at the periphery. The next examination, taken about one month after the second, shows a rather clear-cut, round shadow of considerable density centrally, with indefinite, streaky density extending peripherally.

Dr. Adams: Can we stop here for a moment? This first film shows bilateral apical tuberculosis, with a lesion of some sort in the base, which subsequently showed a cavity. Later, this cavity apparently had filled and became invisible. Is that right, Dr. Wyman?

Dr. Wyman: The central area is denser on the third film. It may be cavity filled with fluid or something that has grown there.

Dr. Adams: Is the third film to be regarded as a healing process compared to the first film? In other words, is it a tuberculous lesion that is becoming fibrotic?

Dr. Wyman: I cannot say that. There is no definite wall about the rarefaction as one usually sees in cavities in tuberculosis. This later density is too sharply defined and homogeneous for the usual tuberculous lesion of this sort. I am not able to picture in my own mind how this thing has come about.

Dr. Adams: That makes two of us.

Dr. Wyman: The next examination, done three months after the original, shows about the same picture that we see on the first observation. This changes little, if any, at the next examination four

months later, which is just about three weeks before he entered this hospital. Finally, there is a definite change in the appearance of the lesion, which is now more widely spread, running down to the costophrenic sinus and showing areas of rarefaction in the upper portion.

The bronchi can be fairly well seen. The lateral view shows that the lesion lies in the base of the right lower lobe far posteriorly. I do not know how much the apparent increase in size is due to hemorrhage in and about this lesion.

DR. ADAMS: There is no sign of foreign body?

DR. WYMAN: Nothing that I can see — no opaque foreign body, at any rate.

DR. ADAMS: Are his rib spaces narrowed? Is there any evidence of collapsed lung in the affected area?

DR. WYMAN: I do not believe so. One can see the major fissures in the anterior portions of the lungs, suggesting little or no collapse in the lower lobe.

DR. ADAMS: It does not look like the picture one sees in coccidiomycosis? Although you say that the cavity wall is thinner than generally seen in tuberculosis, it is not so thin as that which surrounds the cavity of coccidiomycosis?

DR. WYMAN: I do not know much about coccidiomycosis.

DR. ADAMS: Neither do I, but I have seen some. There is virtually no reaction around the cavity.

Bronchoscopy showed a lesion. But nothing is said about obstruction, and the biopsy demonstrated only blood clot. Following this procedure there was a good deal of bleeding.

I am frank to say that I cannot make a diagnosis. The patient once had active tuberculosis, which was apparently arrested. Then he developed a lesion in the base. At first this must have been regarded as fluid because he was tapped several times. Then he was studied for bronchial obstruction, but no definite evidence of this is recorded. It would be easier if we could presuppose that the high diaphragm was due to collapsed lung, but one cannot assume that it was because the homolateral phrenic nerve had previously been crushed.

Dr. King has told me that the effects of phrenic-nerve crush usually endure about six months; in perhaps 15 per cent of cases the nerve may not regenerate at all, provided a thorough crush is done.

DR. KING: That is the figure usually quoted.

DR. ADAMS: It seems reasonable to assume that the lesion was not collapsed lung secondary to bronchial obstruction or phrenic crush but was in the lung itself. The patient had recently had frequent small hemoptyses. This is not the type of hemoptysis usually seen in tuberculosis. Frequent small hemoptyses bespeak bronchiogenic tumor. We have nothing to substantiate a diagnosis of foreign body. The disease could have been adenoma of the bronchus; it could also have been carcinoma of the bronchus. I am relatively certain that the diagnosis was not made prior to operation but that the decision to operate was based on the impression that there was a possibly removable lesion. I can remember in this clinic about a year ago hearing Dr. King struggle with one of these cases on which Dr. Sweet had operated; my recollection is that both of them said one cannot predict whether a lesion, such as this, is tumor or localized tuberculosis. On the whole, it seems to me most logical to say that this was a tuberculous lesion because we know that the patient had had active tuberculosis. To be sure, no matter which diagnosis one grabs, the answer is always the other. We have a spreading lesion with cavitation in a person known to have had active tuberculosis. We have no definite evidence of bronchial obstruction such as one encounters with adenoma or carcinoma. Cavitation with the two latter is unusual except in the presence of total obstruction. On the other hand the absence of fever and systemic disturbances such as loss of weight and strength is a differential point against active and spreading tuberculosis. Because I have to make a diagnosis, I would put my money, chiefly because the patient has tuberculosis elsewhere, on a tuberculous lesion, but would not be surprised if it turned out to be bronchiogenic tumor.

DR. KING: This description of the bronchoscopy worries me. All they say is a "cherry-red lesion." We have no idea about the size, shape or consistence.

DR. MALLORY: Did you do the bronchoscopy, Dr. Davenport?

DR. LOWREY F. DAVENPORT: There was in the posterolateral basal segment of the right lower lobe a small, red lesion, which looked like an adenoma. It was in the bronchus so that it could just be seen faintly, and in grasping the area with the forceps the material was taken out following which there was a gush of blood. The description is not correct. You recall, Dr. Mallory, that there were a few cells in the slide, and there was some difference of opinion whether there was enough material to make a diagnosis. It was your opinion that they were tumor cells. I thought from the appearance that probably it was an adenoma, purely because of the bleeding and the suggestive evidence that the bulk of it lay outside the bronchus. Perhaps I was seeing only a small area of infiltrated mucosa with blood clot.

DR. KING: Was a study done for tumor cells?

DR. MALLORY: Just on the bronchoscopic washings. There were questionable cells mixed in with blood clot from bronchoscopic aspiration.

DR. KING: Dr. Soutter says that he thinks it was done and was negative.

DR. WYMAN: From my point of view I cannot exclude tuberculosis, but I think it is an unusual picture and I had leaned toward tumor, primary bronchiogenic and less likely degenerated adenoma.

DR. KING: You and Dr. Davenport agree, but I think I would read tuberculosis in the second film from the left. I know the answer, so I am prejudiced.

DR. WYMAN: It looks like it, but the next film does not.

DR. KING: That is true.

DR. DAVENPORT: The cavity is not like tuberculosis.

DR. WYMAN: It does not look like it to me.

DR. ADAMS: But it is a cavity in a patient known to have had tuberculosis. That is why I am "hanging my hat" on tuberculosis, but no doubt I have picked the wrong hook.

CLINICAL DIAGNOSES

Pulmonary tuberculosis, right upper lobe.
Carcinoma, right lower lobe.

DR. ADAMS'S DIAGNOSIS

Pulmonary tuberculosis, right upper and lower lobes.

ANATOMICAL DIAGNOSES

Bronchiogenic carcinoma, right lower lobe.
Pulmonary tuberculosis, healed right upper lobe, active right middle and lower lobes.

PATHOLOGICAL DISCUSSION

DR. MALLORY: This is the kind of case to give a clinician whom in the past you have treated very badly.

DR. ADAMS: So you keep on doing the same.

DR. MALLORY: No. It is a case on which he cannot be wrong!

This man had both cancer and tuberculosis. As you can see from the photograph (Fig. 3) the upper lobe is extraordinarily shrunken and consists only of a mass of dilated bronchi embedded in dense scar tissue. The present picture is that of localized bronchiectasis. In that area I can find neither grossly nor microscopically any evidence of active tuberculosis. The middle lobe, in contrast, is considerably enlarged. Scattered throughout it are many very small, firm, dense, active tuberculous lesions, but I am afraid they are too small to be visible in the picture. The main tumor mass in the lower lobe is a highly differentiated epidermoid carcinoma obviously arising from the lobar bronchus, but all around the tumor, especially toward the base, is active tuberculosis. We do not doubt that he had a cavity, but we did not find any at the time of resection. It may well have filled in with tumor.

DR. ADAMS: What was the rationale of operation?

DR. LAMAR SOUTTER: Dr. Sweet operated on him, and our opinion preoperatively was that the patient certainly had tuberculosis. We did not believe it was active in the presence of two negative sputum examinations; he had no high temperature, elevated white-cell count and so forth. We believed that the most logical explanation for the lesion's increase in size was carcinoma. When Dr. Sweet opened the chest he thought pneumonectomy was the only possible operation because the amount of tissue left behind would not be valuable. Leaving the middle lobe in would be technically difficult and not of any value, and it would be much better to remove the whole lesion.

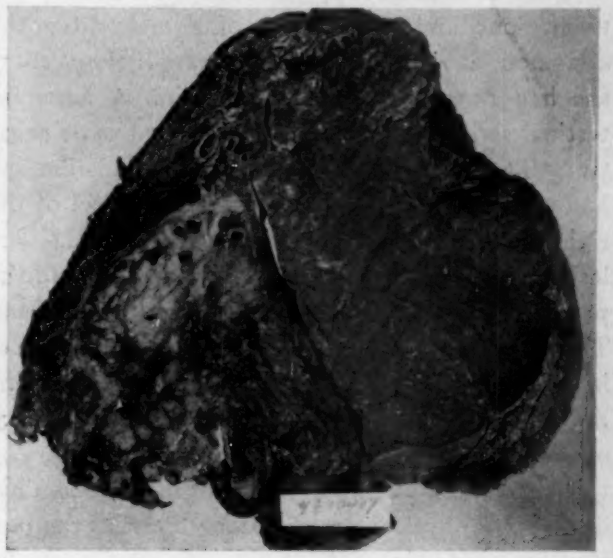

FIGURE 3.

DR. WYMAN: Was there hemorrhage about the lung adjacent to the tumor?

DR. MALLORY: Nothing very striking was noted.

CASE 35022

PRESENTATION OF CASE

A forty-one-year-old Jewish housewife was admitted to the hospital because of increasing swelling of the abdomen.

Three months before admission the patient noted some discomfort and pain in the left upper quadrant, which occasionally radiated across the abdomen to the right midabdomen. One month before admission she noted an increasing swelling of the abdomen, with a mass in the left side. The mass became acutely tender for a week, and then the tenderness subsided. She gave a past history of having had an appendectomy at the age of twenty-one and an excision of a mole from the abdomen at thirty-one. Six years before entry she had noted some epigastric pain. A gastrointestinal series at that time was reported to be negative. Two years before the present admission she had a pigmented lesion on the lateral aspect of the right ankle excised, and the defect grafted. The lesion measured 1.5 by 3.5 cm. in diameter, and the pathological diagnosis was malignant melanoma. There were two questionably enlarged lymph nodes in the right groin, and four weeks later a right radical groin dissection was done. Pathological examination showed no evidence of cancer. At this time there was no evidence of intra-abdominal disease on physical examination. Pelvic examination was not done.

On physical examination the abdomen was protuberant, and there was a huge, fixed, round mass in the region of the spleen. The uterus contained several fibroids. There was no palpable lymphadenopathy. The blood pressure was 130 systolic, 80 diastolic.

Laboratory examination demonstrated a red-cell count of 3,370,000, with a hemoglobin of 9.2 gm., and a white-cell count of 10,400, with a normal differential. The urine was normal. Vaginal smear was negative for tumor cells.

X-ray examination of the abdomen, including a pyelogram, suggested a large, ill defined, intraperitoneal mass in the left midabdomen. The stomach was displaced upward and to the right, as were several loops of small bowel. There was no definite calcification in the mass.

An operation was performed.

Differential Diagnosis

Dr. Fred A. Simmons: It would be helpful to know the duration preoperatively of this pigmented lesion. The lesion is described as measuring 1.5 by 3.5 cm. in diameter. It occurred to me in reviewing this case that it would often be valuable in these exercises to have preoperative and postoperative photographs in cases with superficial lesions. These would help characterize the lesion and also aid in evaluating the extent of the operation. This lesion was approximately average in size for a malignant melanoma, since the mean is 3 cm., according to Taylor and Nathanson.[1]

A right radical groin dissection was done. It would be valuable to know whether this dissection included removal of the lymph nodes up to the bifurcation of the external and internal iliac vessels. The pathological examination of the nodes showed no evidence of metastasis. A careful search of the current literature and two texts on the subject of cancer failed to emphasize a point that should be brought out here. The disease and other malignant neoplasms often skip the normal distribution into the adjacent nodes, and the disease has often progressed into the abdominal or thoracic cavity while the adjacent lymph nodes are reported to be normal.

It would be of interest to know if the physical examination was done by a medical man or a surgeon, for the medical man often finds spleens that the surgeon does not report. The next sentence implies that the physical examination must have been medical, for it says "no pelvic examination was done." The protuberance may have been due to ascites, but there is no further mention of this.

A vaginal smear was negative for tumor cells. I think we may assume that the patient entered this time on the Gynecologic Service.

X-ray examination of the abdomen included a pyelogram. It would be interesting to know if the roentgenologist was willing to express an opinion whether the large mass was intraperitoneal or retroperitoneal. It would be more definitive if "large" could be modified by some measurement. It would be a great help here to have had a barium enema. The absence of calcification would tend to rule out dermoid cyst.

According to previous exercises in this room the negative history of gastrointestinal, genitourinary, gynecologic and neuromuscular systems implies that such history was negative and, therefore, not reported. This leaves us with a lesion that, for lack of any other involvement, must have been retroperitoneal, adrenal or possibly splenic. For the sake of brevity I will omit consideration of the usual medical causes for splenomegaly and can probably

safely omit discussion of trauma of the spleen. If the enlargement was not noticed two years before, it must have been a rapidly growing neoplasm. Since it is almost a 75 per cent bet that the findings in this case will be that of metastatic melanotic sarcoma, I think it would be well to review some of the observations about this disease. According to Taylor and Nathanson,[1] this tumor metastasizes early and by way of both the lymphatics and blood stream. In their 265 cases only 25 per cent had five-year cure, 56 per cent of the primary cases had lymph-node metastases, and 74 per cent of the secondary cases had lymph-node disease. Pack,[2] of New York, finds 50 per cent lymph-node involvement in cases submitted to prophylactic resection. De Cholonky,[3] in 1941, studied 117 cases from the New York Post-Graduate Hospital and states "melanoma is invariably fatal if not controlled by surgery"and found metastatic disease occurring anywhere from three months to thirteen years after onset, while death occurred from six months to eleven years. His survival rate was more pessimistic — 42.3 per cent for the five-year group but only 9.2 per cent for ten-year survival. Before the pessimistic aspect of this becomes too dismal it might be well to mention 2 cases of personal observation that have survived eight to ten years following a lesion on the fourth toe and another, in a doctor's wife, picked up early on the great toe in which the patient remained well following radical excision of that tumor and groin dissection. It is possible that the patient in the case under discussion had a bizarre finding such as an ovarian cyst on a long pedicle lying in the left upper quadrant. The most likely reason for the operation must have been an attack on the spleen itself or merely exploration for diagnostic purposes.

Unless a totally different neoplasm was discovered at this operation, I would expect the findings to be those of extensive metastatic melanotic sarcoma involving the retroperitoneal area and possibly other abdominal organs. Dr. Smithwick had a case in this hospital recently with a small primary lesion on the right upper arm, autopsy two years later showing the disease involving the lungs, the liver, the kidneys and the small intestine. I do not know of any cases that include splenic involvement, nor did I find any in the literature, but I understand that there is one such case in a male patient in this institution.

Clinical Diagnosis

Ovarian cyst?

Dr. Simmons's Diagnosis

Metastatic melanotic sarcoma.

Anatomical Diagnoses

Metastatic melanotic sarcoma.

Pathological Discussion

Dr. Tracy B. Mallory: It was believed on the wards that there was sufficient possibility that this large abdominal mass was something other than metastatic melanoma to warrant exploratory laparotomy. The patient was operated on with a preoperative diagnosis of "question of ovarian cyst." As soon as the abdomen was opened considerable quantities of serosanguineous fluid escaped through the incision.

As the abdomen was explored great masses of metastatic tumor were found. They appeared to be both retroperitoneal and intraperitoneal, and tumor was present in the omentum, the mesentery and in the liver. Biopsies from several areas all showed malignant melanoma.

References

1. Taylor, G. W., and Nathanson, I. T. *Lymph-Node Metastases: Incidence and surgical treatment in neoplastic disease.* 498 pp. New York: Oxford University Press, 1942. Pp. 113-126.
2. *Treatment of Cancer and Allied Disease.* Edited by G. T. Pack and E. M. Livingston. 3 vol. 2598 pp. New York: Paul B. Hoeber, Inc., 1940.
3. DeCholonky, T. Malignant melanoma: clinical study of 117 cases. *Ann. Surg.* **113**:392-410, 1941.

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ALPHA AND OMEGA

IN INFANCY and crabbed age an immortality and a fate are presented to mankind. The former, because full of promise, is easier to contemplate and also easier to serve, as witness the readiness with which funds, public and private, are obtained for infant and child welfare, and the increasing scope of effective medical care in this field. As infant mortality has decreased, however, and an ever larger proportion of survivors, healthy to start with, is kept in health, the inevitability of old age increases, but not necessarily its miseries.

In this issue of the *Journal* Clifford recounts the achievements of preventive medicine in the life of the embryo and fetus as well as in the newborn child. The old wives' tales of a child being "marked" by an experience of the pregnant mother have here modern scientific support. Infections, attempted abortions and poor diet may mark an unborn child with a congenital malformation and may predispose him to the hazards of prematurity or to death by miscarriage or stillbirth. Also, the infant may receive favorable marks from the moment of conception by appropriate medical supervision. In the prenatal period not only are the ill effects of infection, trauma, incompatible blood and inadequate diet prevented but also the mother in a more positive sense may be prepared psychologically for the nursing and care of her child. In this particular the "rooming in" system whereby mother and baby may remain together returns them to the relations of the home and yet affords the scientific protections of the modern hospital.

If babies do not arrive naturally and full-fledged, trailing clouds of glory, but require hard, precise supervision for nine months after the time of conception, neither is the traditional misery of old age as inevitable as supposed. For eight years a geriatric clinic in Boston has been stating the medical problems of old age, asking in what ways health and disease differ in the evening of life and what one does about them. Happily, Monroe, also in this issue of the *Journal*, has made available the benefit of his experience. It appears that, in the second childhood as in the first, nutrition is extremely important, that no play makes these old Jacks the dull boys that they so often are, and that unoccupied old minds like their young counterparts get into slothful or other bad habits.

The extension of individual preventive medicine into the fetal period and the support it gives to certain of Grandma's observations may be viewed with great satisfaction. It is a source of gratification that in lying-in hospitals mother love at last is asserting itself over the nursing supervisor's efficiency and the pediatrician's feeding schedule. It is not so gratifying to realize that one of the few manifestations of filial piety in modern life is the development of geriatrics as a medical specialty, pleasing as it is to contemplate the renewed interest in this phase of medical care.

ARE WAR YEARS GOOD YEARS?

SHORTLY before his death, the late John Winant asked an audience: "Are you doing as much for peace as you did for this country and civilization in the days of war?" It is a question well worth pondering. It leads one eventually to consider the incentives for working actively toward peace. Bizarre as it may seem, such incentives do not appear to be very clear in the minds of the American people. To a European whose home was destroyed, whose business was disrupted and who may have been starved, incarcerated, or tortured during the recent war, peace is obviously better than war if only for purely materialistic reasons. To the American who suffered no such privations the evidence that peace is preferable to war may be far less vivid. In fact, according to a recent analysis,* most statistical indexes indicate that war years are more prosperous than peace years. Industrial production, factory employment, hourly earnings and the gross national product all began to rise about 1937 and continued to rise steadily during the war years. They seem to have been influenced little, if any, by the war. The indexes ordinarily used to measure business cycles (bank clearings outside New York City, freight-car tonnage, industrial production, business failures and wholesale commodity prices) show that the periods covered by World War I and II have all the earmarks of prosperity. Public assistance (relief) and business failures declined precipitately from 1940 onward. Business profits, like production, "were greater than usual in the war year 1917, and again the years of the second world war, 1942-45." Indexes, indicative of social conditions, such as marriages, births, deaths and divorces, seem to have been very little affected by the war and certainly were not adversely affected. The statisticians were able to produce very little evidence that war is economically undesirable, although their data do show that taxes and the public debt went up while public works declined during the war years. Nor does their evidence touch on the obvious fact that most of our enormous wartime production was not available or suitable for civilian use.

*Ogborn, W., and Adams, J. Are our wars good times? *Scient. Monthly* 67:23-33, 1948.

In spite of the incompleteness of purely financial evaluations of the effects of war, such reports unquestionably exert an insidious influence on many people. Confronted with such evidence and recalling his high pay and full employment during wartime what is the American worker to conclude? The businessman also, viewing his increased profits and the seller's market, can hardly regard war as altogether bad. It is perhaps too much to expect these groups to look beyond such statistics and their own wartime business experience to see the unmeasured and perhaps incalculable damage wrought by war on a participating population, no matter how far removed from the actual fighting. The authors of the treatise in question candidly state: "The positive association of good times in the United States during the war probably has a bearing upon our willingness to engage in another war." One might put it even more strongly.

Physicians, especially those who served in the armed forces, are in a better position to penetrate the veil of material prosperity and visualize the malignant effects of war. Like the public debt, the disruption of scientific education at all levels and, to some extent, of scientific research will weigh heavily in the future. The vast wastage, not only of materials but especially of scientific talents and skills, was painfully apparent, unavoidable though such wastage may have been. The tangible and intangible effects of wartime fear and insecurity should be apparent to the physician, of all people. These and many more features, whether the statistician's indexes uncover them or not, must ultimately be taken into account by everyone, doctor or layman.

Finally, as the authors point out, this country may not escape vast internal damage if it engages in another war. Whether war can be avoided is problematic. In any case, the country should not enter on any such project without full and sober consideration of the evils of war that business and financial statistics do not reveal. The physician has first-hand knowledge of many of these relatively occult features, and if he does his part to make the layman aware of them, and to keep them crystal clear in his own mind, he can answer Mr. Winant's question with a resounding yes!

SURVEY OF MEDICAL EDUCATION

BEGINNING with the new year, the Council on Medical Education and Hospitals of the American Medical Association and the Association of American Medical Colleges have put on foot a three-year joint survey of medical education in the United States. To further this project a committee of seven has been appointed, composed of leaders in medical education, and Dr. John E. Deitrick, of New York, has been selected as the full-time director of the survey. Dr. Deitrick, a graduate of Johns Hopkins University School of Medicine, is associate professor of medicine at the Cornell University Medical College, and medical director and director of postgraduate instruction of the Second Medical Division, Bellevue Hospital.

The objects of the study, as stated by the committee, are to evaluate the present programs and determine the future responsibilities of medical education in its broadest aspects, in order to improve medical education better to meet the needs of the American people for the prevention of disease, the expedition of convalescence and the maintenance of health; to assess the degree to which medical schools are meeting the needs of the country for physicians; to promote the advancement of knowledge in the field of medical science; and to inform the public concerning the nature, content, and purposes of medical education.

The present survey is the third that has been made in forty years. The first resulted in the Flexner Report, published in 1910 by the Carnegie Foundation for the Advancement of Teaching; the second resulted in the Weiskotten Report, published ten years ago.

This timely survey will undoubtedly consider various factors that concern the future of medical education — the problem of preparedness for national emergencies, the social aspects of medicine in all their ramifications, the place that medical practice will occupy, and the sources of the funds with which the costs will be defrayed.

The world has become a social laboratory in which medicine must play its part in interpreting the reactions.

HISTOPLASMOSIS IN MASSACHUSETTS?

PREVIOUSLY in these columns* mention was made of the possible significance of histoplasmosis as the cause of the unexplained cases of disseminated areas of calcification visible in x-ray films of the lungs in nonreactors to tuberculin who give positive skin reactions to histoplasmin. Attention was called to the recent surveys, particularly those carried out in Kansas City, Missouri, and in Tennessee, which uncovered a large number of such persons. Studies among nurses also revealed a high incidence in the eastern central area of the United States, and the frequency of their occurrence diminished progressively in proportion to the distance from this area. It was noted at that time that histoplasmosis was not known to occur in New England but that it had been reported from areas as close as New York and Washington, D. C.

In a letter from Mautner, which appears elsewhere in this issue of the *Journal*, evidence is presented suggesting that infections with histoplasma might indeed occur in an unrecognized form in Massachusetts. The evidence, to be sure, is far from conclusive. It is based upon the demonstration of local reactions in the skin of patients at the Wrentham State School following intracutaneous injection of histoplasmin. Of 200 patients tested with 0.1 cc. of a 1:1000 dilution, only 2 showed mild reactions that were delayed, and injection of a larger amount — namely, 0.1 cc. of a 1:100 dilution — yielded 19 reactors among 100 patients, and the reactions were more intense and occurred earlier. All but one of the histoplasmin reactors showed positive tuberculin tests. The negative tuberculin reactor who was tested with the smaller amount, and 4 of those who reacted to the larger amounts of the histoplasmin showed some areas of pulmonary calcification in roentgenograms of the chest. Mautner's findings, though inadequately controlled and not proving conclusively that his reactors had histoplasmosis, suggest that this infection should be considered in the differential diagnosis of patients with diffuse pulmonary lesions in which other more likely diagnoses can be ruled out.

*Editorial. Nontuberculous pulmonary calcification. *New Eng. J. Med.* 237:171, 1947.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CARTER — Arthur C. Carter, M.D., of South Dartmouth, died on November 26. He was in his forty-ninth year.

Dr. Carter received his degree from Tufts College Medical School in 1936. He was formerly superintendent of Sassaquin Sanatorium in New Bedford.

His widow, his father and two daughters survive.

CURRIER — W. Eugene Currier, M.D., of Leominster, died on November 23, 1948. He was in his seventy-eighth year.

Dr. Currier received his degree from Harvard Medical School in 1898. He was formerly school physician in Leominster and a member of the staff of Leominster Hospital.

His widow and two nephews survive.

GEORGE — Arial W. George, M.D., of Wellesley Hills, died on December 23. He was in his sixty-seventh year.

Dr. George received his degree from Tufts College Medical School in 1906. He was radiologist at Brooks Hospital, Brookline, Glover Memorial Hospital, Needham, and Massachusetts Institute of Technology. He was a former chancellor of the American College of Radiologists, a member of the New England Roentgen Ray Society, American Roentgen Ray Society and Radiological Society of North America, Inc., and a fellow of the American Medical Association.

His widow, two sons and a sister survive.

OVERLANDER — Charles L. Overlander, M.D., of Boston, died on December 16. He was in his seventy-sixth year.

Dr. Overlander received his degree from Harvard Medical School in 1905. He was a member of the American College of Physicians and a fellow of the American Medical Association and was director of the Pathological Laboratory at Brooks Hospital, Brookline.

His widow and a brother survive.

QUIST — F. Julius Quist, M.D., of Worcester, died on December 20. He was in his seventy-fourth year.

Dr. Quist received his degree from Rush Medical College in 1905. He was a fellow of the American Medical Association.

His widow, a brother and a nephew survive.

SILVERSTEIN — Maurice L. Silverstein, of Boston, died in the military service on February 16, 1946. He was in his forty-eighth year.

Dr. Silverstein received his degree from Boston University School of Medicine in 1923.

MISCELLANY

AWARD TO NATIONAL INSTITUTES OF HEALTH

Dr. Rollo E. Dyer, director of the National Institutes of Health of the United States Public Health Service, received on December 7, 1948, in behalf of his organization the 1948 Award of Distinction from the American Pharmaceutical Manufacturers' Association in recognition of the Institutes' "great contributions to public health through fundamental medical research for the profound benefit of mankind." Presentation of the award was made by Dr. Ernest E. Irons, president-elect of the American Medical Association.

The National Institutes of Health include the National Cancer Institute, the National Heart Institute, the National Institute of Dental Research, the National Institute of Mental Health, the Institute of Experimental Biology and the Institute of Microbiology.

CANCER RESEARCH UNIT AT COLUMBIA

Columbia University has announced its plans for a $2,000,000 cancer research unit to be constructed on top of the present Vanderbilt Clinic at the Columbia-Presbyterian Medical Center. Half the construction cost will be provided by the National Advisory Cancer Council and half by Columbia University.

AMERICAN COUNCIL ON RHEUMATIC FEVER OF AMERICAN HEART ASSOCIATION

Dr. Rustin McIntosh, director of the Pediatric Service, Presbyterian Hospital, and Carpentier Professor of Pediatrics, Columbia University College of Physicians and Surgeons, has been elected 1949 chairman of the American Council on Rheumatic Fever of the American Heart Association.

Mr. Lawrence Linck of Chicago was elected vice-chairman.

Newly elected members of the Council's Executive Committee include, in addition to Dr. McIntosh, Mr. A. W. Robertson (*ex officio*), chairman of the Board of the American Heart Association, Pittsburgh; Dr. Hugh McCulloch, St. Louis; Dr. Walter Bauer, Boston; Dr. David D. Rutstein, Boston; Dr. Edward Harmon, Valhalla, New York; Dr. M. J. Shapiro, Minneapolis; Dr. T. Duckett Jones, New York City; Dr. Homer F. Swift, New York City; and Dr. George M. Wheatley, New York City.

QUARTER, QUARTER, WHO HAS THE QUARTER?

S. 1320 [Wagner–Murray–Dingell Bill], Section 204.

(a) Every individual shall be eligible for benefits under this title throughout any benefit year if —

(1) he has received (or, in the case of incomes from self-employment, has accrued) —

(A) not less than $150 in wages during the first four of the last six calendar quarters preceding the beginning of the benefit year; or

(B) not less than $50 in wages in each of six calendar quarters during the first twelve of the last fourteen calendar quarters preceding the beginning of the benefit year (not counting as one of such fourteen calendar quarters any quarter in any part of which the individual was under a total disability which continued for six months or more);

(2) he is entitled, for the first month in the benefit year, to a benefit under title II of the Social Security Act, as amended, or to an annuity under the Civil Service Retirement Act, as amended; or

(3) he is on the first day of the benefit year a dependent of an individual who is eligible under paragraph (1) or paragraph (2).

OUTPATIENT TREATMENT OF VETERANS

Nearly 2,000,000 veterans received outpatient treatment from the Veterans Administration during the fiscal year ending June 30, 1948. The treatments were given at regional offices, hospitals and clinics, and by private physicians co-operating with the Veterans Administration in providing home-town care for veterans with service-connected disabilities.

Treatments averaged 3 per veteran, or a total of 5,223,680. Patients treated numbered 1,937,842.

Private physicians treated 761,185 veterans, or about 40 per cent of the total. The physicians were paid $11,437,870 for 2,735,450 treatments, or an average of $4.18 per treatment or $15.03 per veteran undergoing medical care.

Veterans Administration staff doctors during the year treated 1,176,657 individual veterans, providing a total of 2,498,230 treatments.

CORRESPONDENCE

HISTOPLASMIN REACTIONS

To the Editor: The publications concerning histoplasmosis have proved the importance of this interesting infection. Up to this time we at the Wrentham State School have had no possibility of publishing our experiences.

In the fall of 1946, we were supplied with a small amount of extract by Dr. Herman Vollmer. In our first series 0.1 cc. of a solution of 1:1000 was administered intracutaneously to 200 patients, 2 of whom showed, on the third day, a mild local reaction, which disappeared on the fourth day. One of them had a positive Pirquet reaction. In the other, a seventeen-year-old boy, the Pirquet reaction was negative, and x-ray examination showed a peculiar appearance of the lungs, resembling tuberculosis.

In January, 1947, we were supplied with a stronger extract of 1:100; 0.1 cc. of this solution was administered to 100 patients. Nineteen showed a local reaction on the following day. In 9 of them the reaction was quite strong, but only 6 were positive on the next day. All 19 patients showed a positive tuberculin reaction. X-ray films of 4 showed calcification of the lung, which could easily have been Ghon nuclei or calcified lymph nodes. One film even looked somewhat peculiar for tuberculosis.

The examinations have not been continued, since it was difficult to obtain the extract at that time. Nevertheless, it seems that isolated infection with histoplasma, without severe sequel, occurs in Massachusetts.

The patients examined were in the care of the Wrentham State School, and the last series of 100 were in a building where the older women live.

HANS MAUTNER, M.D.

Wrentham State School

HOW TO MAKE FRIENDS AND INFLUENCE PEOPLE

To the Editor: The following safe advice, presented to the meeting of secretaries and editors at St. Louis, speaks for itself:

FRISCO DOCTOR PRESENTS HIS OWN PROGRAM. In this day and age when everybody is talking himself hoarse about medical plans and programs, Dr. Anthony B. Diepenbrock, of San Francisco, comes up with his own 13-point health program which, he says, "might be interesting to our colleagues":

1. Continue to sit on your fat derriere and do nothing.
2. Be apathetic and, like 5,000,000 registered Republican voters who failed to vote, do not bother to make your opinion known. If you think, as they did, that your opinion or your vote is not worth anything, the opposition will agree with you and act accordingly, as they have.
3. Write an occasional letter to your congressman, tell him off, and then explain proudly to the intern in the surgical dressing rooms how smart you are and what a stinker your congressman is.
4. Tell everybody you see that the gag is up, and we might as well prepare for the inevitable.
5. Moan and groan and issue explosive and unprintable epithets.
6. Refer to your medical leadership as a group of impotent, ineffective and bumbling ignoramuses.
7. Make speeches before sympathetic lay audiences, and convert those who already believe in free enterprise.
8. Don't bother to tell your county society heads, your state society heads, or your national association heads what you want them to do. Expect them to find a way for you without your guidance.
9. Scream about high medical society dues and forget that our friends in the trades unions demand many times what we pay: in other words, make the situation as difficult as possible, then grumble about it.
10. Oppose any program developed by the majority of your colleagues because it demonstrates your superior wit and your general greatness.
11. Remain superbly and learnedly dignified when Joe Doakes asks why you oppose state medicine. Brush him aside with any insult you can think of. Joe will like you for that.
12. Don't bother to use the selling methods which actually bring messages before the public. Continue to depend on occasional radio feature programs. Billboard advertising, newspaper advertising, national magazine advertising, radio advertising and above all, continuous and daily radio spot programs over national hookups and all such like are too commercial, too troublesome, too expensive and too undignified: don't use them.
13. Above all, disregard the "little guy" — the one with a vote. Tell him nothing; push him around. He doesn't know anything anyhow.

H. QUIMBY GALLUPE, M.D.

8 Fenway, Boston

SOUTH CAROLINA LEADS

To the Editor: In the December 2 issue of the *Journal*, I read with interest your editorial on the Massachusetts Medical Benevolent Society, "the oldest of its kind in continuous existence in the United States," calling attention to its ninety years of useful and beneficent activities. I now respectfully direct your attention to Charleston, America's Most Historical City, where, on January 12, 1949, The Society for the Relief of the Families of Deceased and Disabled Indigent Members of the Medical Profession of the State of South Carolina, today referred to as the Widows and Orphans Society, is having its Centennial Banquet. In its early days the treasurer's books carry the name of the Medical Benevolent Society. The Society was organized in 1848 and was incorporated on December 19, 1849. Annually, it has contributed to its beneficiaries. One reason for its continued growth is a wise provision in the Constitution to the effect that a fourth of the annual income must be reinvested. According to its Constitution: "any person of good moral character" may be a member. "The members of the Society shall annually assemble and dine or sup together, in the City of Charleston, on the second (2nd) Wednesday of January in every year." The Stewards are to provide and the Treasurer is to pay for the supper.

LEON BANOV, JR., M.D.

104½ Rutledge Ave.,
Charleston 16, S. C.

NOTE: Apologies and congratulations to the medical fraternity of South Carolina. — ED.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

War, Politics, and Insanity. By C. S. Bluemel, M.A., M.D., M.R.C.S. (Eng.). 8°, cloth, 121 pp. Denver: The World Press, Incorporated, 1948. $2.00.

The author in this monograph discusses the psychologic qualities of political leadership and the disorders of personality with which aggressive leadership is commonly associated.

Modern Clinical Psychiatry. By Arthur P. Noyes, M.D., superintendent, Norristown State Hospital, Norristown, Pennsylvania. Third edition. 8°, cloth, 525 pp. Philadelphia: W. B. Saunders Company, 1948. $6.00.

This third edition of a textbook, first published in 1934 and revised in 1939, has been largely rewritten, and three chapters have been added on psychotherapy, shock and other physical therapies and child psychiatry. The material on the psychoneuroses has been amplified, and that on psychosomatics has been extended. The book is based on lectures originally presented to senior medical students. The material is well organized and well written, and the publishing is excellent.

Subacute Bacterial Endocarditis. By Emanuel Libman, M.D., and Charles K. Friedberg, M.D., adjunct physician, Mt. Sinai Hospital, New York City. Edited by Henry A. Christian, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (Am. Med. Assoc.). 8°, cloth, 113 pp., with 19 illustrations. New York: Oxford University Press, 1948. $3.50. Reprinted from *Oxford Loose-Leaf Medicine* with the same pagination.

This monograph is a reprint from the *Oxford Loose-Leaf Medicine*, published in book form, making it available to interested physicians who do not have the system. The text reflects the latest information on the subject. A large bibliography concludes the text. The publishing is well done.

Chronic Ill-Health, Relieved by Drainage of the Para-Nasal Sinuses. By Rosa Ford, M.B. (Lond.), D.O. (Oxon.). 12°, cloth, 104 pp., with 13 illustrations. London: Henry Kimpton, 1948. 6/6 net.

The author, in this short monograph, presents 47 cases of chronic disease relieved by drainage of the nasal sinuses. The diagnosis of the condition was made largely through an intensive study of the fields of vision. A short bibliography and a list of cases conclude the text. There is a good index. The publishing is excellent. The price is reasonable. The volume should prove interesting to ophthalmologists and rhinologists.

Modern Trends in Dermatology. Edited by R. M. B. MacKenna, M.A., M.D. (Camb.), F.R.C.P. (Lond.), physician-in-charge, dermatological department, and lecturer in dermatology, St. Bartholomew's Hospital, London, physician to St. John's Hospital for Diseases of the Skin, London, honorary consultant in dermatology to the British Army and examiner in dermatology, Royal Army Medical College. 8°, cloth, 432 pp., with 32 illustrations. New York: Paul B. Hoeber, Incorporated, 1948. $8.50.

This composite work of twenty-three dermatologists presents the modern conception of dermatology in varying aspects. The first chapter constitutes a short history of dermatology, followed by special chapters, including psychologic aspects, problems in tropical and subtropical areas, the prevention of cutaneous diseases (excluding industrial diseases) and the rehabilitation of dermatologic patients. The question of rehabilitation has received needed attention only recently. Bibliographies are appended to the chapters. The type and printing are good, but the use of a coated paper is not justified by the few noncolored illustrations. The volume is recommended for all medical libraries.

The Scientific Paper: How to prepare it; how to write it. A handbook for students and research workers in all branches of science. By Sam F. Trelease, Columbia University. 12°, cloth, 152 pp., with 8 illustrations, 7 tables. Baltimore: The Williams and Wilkins Company, 1947. $2.00.

This is a new edition of the author's *Preparation of Scientific and Technical Papers* published in 1936. The text has been thoroughly revised and largely rewritten. The manual is intended for students and research workers but should prove valuable to physicians who are called on to write papers for publication. It covers the whole field from outlining and writing the paper to proofreading. A good index concludes the volume. It is recommended for all medical libraries.

Medical Hypnosis. Vol. I. *The Principles of Hypnotherapy.* Vol. II. *The Practice of Hypnotherapy.* 8°, cloth, Vol. I, 449 pp.; Vol. II, 513 pp. New York: Grune and Stratton, 1948. Vol. I, $5.50; Vol. II, $6.50.

This comprehensive treatise covers the whole field of hypnotherapy. The second volume is devoted to discussions of hypnosis in the removal of symptoms, in psychobiologic therapy and in psychoanalytic therapy. The work is well published. The set is recommended for large medical libraries and to psychiatrists.

The Skull, Sinuses and Mastoids: A handbook of roentgen diagnosis. By Barton R. Young, M.D., professor of radiology, Temple University Medical School. 8°, cloth, 328 pp., with 141 plates. Chicago: The Year Book Publishers, Incorporated, 1948. $6.50.

This volume is one of a series of handbooks on x-ray diagnosis projected by the publishers. The text is divided into three parts: the skull, the nasal sinuses and the mastoids. The text comprises descriptions of various conditions, each of which is illustrated with a radiographic plate. The type, printing and plate work are good. A bibliography and a good index conclude the volume. The seemingly large price is justified by the large number of plates. This volume and its companions should be in all medical libraries and in the libraries of radiologists.

The Diabetic's Handbook: How to work with your doctor: Treatment by diet and insulin. By Anthony M. Sindoni, Jr., M.D., chief, Department of Metabolism, Philadelphia General and St. Joseph hospitals, chairman, Advisory Committee on Diabetes to director of Department of Public Health, Philadelphia, and chief, diseases of metabolism, St. Francis Hospital, Wilmington, Delaware. With an introduction by Rufus S. Reeves, M.D., director, Department of Public Health, Philadelphia. With a foreword by Charles C. Wolferth, M.D., professor of medicine, School of Medicine, and administrator of the Robinette Foundation for Research in Cardiovascular Disease, University of Pennsylvania, director for cardiology, Professional Services Division, Veterans Administration, and consultant cardiologist to the Jewish Hospital. 8°, cloth, 194 pp. New York: The Ronald Press Company, 1948. $3.00.

This manual for the diabetic patient is the joint work of seven physicians. The material is well written and well organized. The section on foods, documented with a number of tables, comprises sixty-three pages. A good index concludes the volume. The book is well published and should prove useful to patients and their families.

Intracranial Tumors. By Percival Bailey, M.D., professor of neurology and neurological surgery, University of Illinois. 8°, cloth, 471 pp., with 155 illustrations and 16 plates. Second edition. Springfield, Illinois: Charles C Thomas, 1948. $10.50.

This second edition of an authoritative treatise has been revised to include the recent advances in knowledge, and a brief atlas of roentgenographic photographs has been added as an appendix. A comprehensive bibliography concludes the text. There is a good index. The volume is well printed with good type on lightweight, nonglare paper. It is recommended for all medical libraries.

NOTICES

ANNOUNCEMENT

Dr. Arthur L. Hanrahan announces the removal of his office from 45 Bay State Road to 270 Commonwealth Avenue, Boston, for the practice of surgery.

GEORGE F. BAKER CLINIC

The Committee on Diabetes, appointed by action of the Massachusetts Medical Society, has suggested that clinical exercises in diabetes be offered without charge in various hospitals for physicians. To this end the George F. Baker Clinic at the New England Deaconess Hospital offers exercises on Monday and Friday of each week. The schedules are as follows.

Monday, 8:00–9:00 a.m., Second Floor, New England Deaconess Hospital. Case Presentations in Diabetes and Surgery of the Extremities.

Friday, 8:00–8:15 a.m., Second Floor, New England Deaconess Hospital. X-Ray Pathology in Diabetes.

8:15–9:00 a.m. Classroom, George F. Baker Building. Case Problems in Treatment of Diabetes and Complications: Pregnancies, acidosis, insulin resistance and so forth.

9:00–10:30 a.m. Medical Rounds for Visiting Physicians.

9:00–10:30 a.m. Instruction in Diet and Urine Testing (for Office Nurses, Technicians or Secretaries Sent by Physicians).

10:30–11:15 a.m. Class Teaching in Diabetes (Physicians, Office Assistants and Nurses are welcome).

SOUTH END MEDICAL CLUB

A regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, January 18, at 12 noon. Dr. Lawrence C. Kingsland, Jr., will speak on the subject "Respiratory Infections in Children." The lecture will be illustrated with lantern slides. All physicians are cordially invited. Luncheon will be served after the lecture, at a cost of 60 cents. Reservations should be made for the luncheon.

MT. AUBURN HOSPITAL

The following public-health lectures will be held at Margaret Jewett Hall, Mt. Auburn Hospital, 330 Mt. Auburn Street, Cambridge, Massachusetts, on Wednesday evenings at 8 o'clock:

January 19. X-Ray in Modern Medicine. Richard Schatzki, M.D.

February 2. The Cancer Problem. Edward A. Cooney, M.D.

February 16. The Heart and High Blood Pressure. Dudley Merrill, M.D.

March 2. Tuberculosis. Lowrey F. Davenport, M.D.

March 16. Surgical Emergencies. Stanley J. G. Nowak, M.D.

These lectures are open to the public.

NATIONAL CONFERENCE ON MEDICAL SERVICE

The National Conference on Medical Service will be held at the Palmer House, Chicago, on February 6. The preliminary program is as follows:

9:00 a.m. Registration; Foyer of Red Lacquer Room Fourth Floor Palmer House.

9:30 a.m. Call to order:

Appointment of Committees.
Address of the President. — E. F. Sladek, M.D., Traverse City, Michigan.

9:45 a.m. Legalized Medical Research.
Medical Problems. — Chris J. D. Zarafonetis, M.D., University of Michigan.
Legal Problems. — George Wakerlin, M.D., University of Illinois.

10:25 a.m. Title to be announced. — James R. McVay, M.D., Kansas City, Missouri; Chairman, Council on Medical Service, A.M.A.

10:50 a.m. Progress of the World Health Organization. — Frank Calderone, M.D., Director, American Office, World Health Organization.

11:05 a.m. Progress of the World Medical Association. — Creighton Barker, M.D., Executive Secretary, Connecticut State Medical Association.

11:20 a.m. Medical Program of the United Mine Workers of America Welfare and Retirement Fund. — Warren F. Draper, M.D., Executive Medical Director.

11:40 a.m. Discussion Period.

12:15 p.m. Subscription Luncheon.

1:00 p.m. The A.M.A. puts on its Fighting Togs. Speaker to be announced.

2:00 p.m. What's Happening in Washington This Week. — James D. Boyle, United Public Health League.

2:30 p.m. Discussion. To be opened by Joseph S. Lawrence, M.D., Director of the Washington Office, A.M.A.

2:40 p.m. Panel Discussion on Postgraduate Education of the Doctor. —
(a) Responsibility of Medical Schools in Continued Postgraduate Education of the Doctor. — George N. Aagaard, Director of Postgraduate Medical Education Program, University of Minnesota.
(b) Function of the State Medical Society in Postgraduate Work. — C. W. Smith, M.D., Harrisburg, Pennsylvania.
(c) Survey Findings on Specialization in Colorado. — Harold I. Goldman, M.D., Denver, Colorado.

3:40 p.m. Discussion Period.

4:00 p.m. Can Corporations Such as Hospitals Legally Engage in the Practice of Medicine? — Wilbur Bailey, M.D., Los Angeles, California.

4:30 p.m. Report of Committees and Election of Officers.

5:00 p.m. Adjournment.
(Note: All papers will begin exactly as scheduled. No speaker will be allowed to speak overtime.)

All physicians are invited.

THE AMERICAN CANCER SOCIETY FELLOWSHIPS IN EXFOLIATIVE CYTOLOGY

At the symposium on exfoliative cytologic diagnostic technics of the American Cancer Society, held in Boston in April, 1948, the opinion was expressed that facilities were urgently needed to train qualified pathologists and clinicians in teaching positions at approved institutions providing residency training in pathology as well as facilities for the training of technicians.

At the same time delegates recommended that the American Cancer Society proceed to engage actively the interest and support of institutions and laboratories in setting up such training programs where the best training facilities appeared to be available. Thus inquiries were sent to fourteen laboratories over the country and, on the basis of their interest and monies available, grants will be made for fellowship training in ten laboratories to support 23 fellows.

The purpose of these fellowships is to provide training in diagnostic technics in exfoliative cytology for qualified pathologists. It is anticipated that trainees will not assume the role of teachers until sufficient personal experience and competence have been acquired.

Fellowships shall be awarded by institutions or laboratories designated by the Society to applicants on the basis of their past training and their intention to teach in their own laboratories diagnostic technics in exfoliative cytology to interested pathologists, clinicians and technicians.

Applicants for fellowships in exfoliative cytology of the American Cancer Society shall be graduates of Class A medical schools of the United States and its territories and of Canada, and be citizens of the United States not over fifty years of age on the next birthday following commencement of fellowship tenure. They shall have completed two years of postgraduate training in pathology and shall conform in other respects to requirements of the institution to which they apply.

Each fellowship shall be awarded for a period of four months. Fellowship training shall begin on November 1, 1948 or as soon as possible therafter. Such fellowships are not subject to renewal.

Stipends will be paid in two sums: the first, a grant to the laboratory for tuition, overhead, and other expenses as outlined to the Society; the second, to the trainee partially to cover his board, room and incidentals for the period of training. The latter sum shall amount to $140 and shall be paid directly to the recipient monthly in advance to avoid payment of income tax for services rendered to the hospital.

Individual applicants for fellowships in exfoliative cytology shall apply directly to institutions where fellowships are available. In no instance shall application be made directly to the American Cancer Society.

The following fellowships are available.

Laboratory	Number	Director
Cornell University Medical College, New York City	6	George N. Papanicolaou, M.D.
Jefferson Hospital, Philadelphia	6	Lewis C. Scheffey, M.D.
University of Oregon Medical School, Portland, Oregon	2	Warren C. Hunter, M.D.
University of California Hospital, San Francisco	2	Herbert F. Traut, M.D.
Michael Reese Hospital, Chicago	2	Otto Saphir, M.D.
Hartford Hospital, Hartford, Connecticut	2	Ralph E. Kendall, M.D.
New York Post-Graduate Hospital, New York City	1	Locke L. Mackenzie, M.D.
Free Hospital for Women, Brookline, Massachusetts	1	Arthur T. Hertig, M.D.
Mayo Clinic, Rochester, Minnesota	1	John R. McDonald, M.D.

(*Notices concluded on page xi*)